UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES,
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 22-JUL-2009

SUBJECT: **Saflufenacil. Revised** Human-Health Risk Assessment for Proposed Uses in/on Legume Vegetables (Crop Group 06), the Foliage of Legume Vegetables (Crop Group 07), Citrus Fruits (Crop Group 10), Pome Fruits (Crop Group 11), Stone Fruits (Crop Group 12), Tree Nuts (Crop Group14), Pistachio, Cereal Grains (Crop Group 15), Forage, Fodder and Straw of Cereal Grains (Crop Group 16), Grapes, Cotton, and Sunflower.

PC Code: 118203	**DP Barcode:** D367317
Decision No.: 389161	**Registration Nos.:** 7969-ETA, 7969-ETI, 7969-ETO, 7969-EIN
Petition No.: 8F7322	**Regulatory Action:** Sec. 3 Registration
Risk Assessment Type: Single Chemical/ Aggregate	**Case No.:** NA
TXR No.: NA	**CAS No.:** 372137-35-4
MRID No.: NA	**40 CFR:** §180.xxx

FROM: Lisa Austin, Ph.D., Toxicologist
George F. Kramer, Ph.D., Senior Chemist
Kelly Lowe, Environmental Scientist
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED, 7509P)

THROUGH: Dana M. Vogel, Branch Chief
RAB 1/HED (7509P)

TO: Kathryn Montague/Joanne Miller, PM Team 23
Registration Division (RD; 7505P)

NOTE: **This updated document supersedes "Saflufenacil.** Human-Health Risk Assessment for Proposed Uses in/on Legume Vegetables (Crop Group 06), the Foliage of Legume Vegetables (Crop Group 07), Citrus Fruits (Crop Group 10), Pome Fruits (Crop Group 11), Stone Fruits (Crop Group 12), Tree Nuts (Crop Group14), Cereal Grains (Crop Group 15), Forage, Fodder and Straw of Cereal Grains (Crop Group 16), Grapes, Cotton, and Sunflower.," (**D349930, dated 28-MAY-2009**). This assessment has been updated to include: **1) revisions to the proposed analytical enforcement method; 2) addition of pistachios; and 3) correction of typos.**

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and

exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed uses of saflufenacil in/on legume vegetables (Crop Group 06), the foliage of legume vegetables (Crop Group 07), citrus fruits (Crop Group 10), pome fruits (Crop Group 11), stone fruits (Crop Group 12), tree nuts (Crop Group 14), cereal grains (Crop Group 15), forage, fodder and straw of cereal grains (Crop Group 16), grapes, cotton, and sunflower. The petitioner is BASF. This is the first food use request for saflufenacil. This is a shared joint review with the Pest Management Regulatory Agency (PMRA) of Canada and the Australian Pesticides and Veterinary Medicines Authority (APVMA). The chronic reference dose is harmonized with Canada and Australia. Also, the residue definition and recommended tolerances are harmonized with Canada and Australia.

A summary of the findings and an assessment of human-health risk resulting from the proposed uses of saflufenacil are provided in this document. The risk assessment and the hazard characterization were provided by Lisa Austin (RAB1), the residue chemistry data review and dietary risk assessment by George Kramer (RAB1), the occupational/residential exposure assessment by Kelly Lowe (RAB1), and the drinking water assessment by Greg Orrick of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration:

Pending submission of revised Sections B and F (see requirements under Directions for Use and Proposed Tolerances) and the submission of reference standards for the saflufenacil metabolites (see requirements under Submittal of Analytical Reference Standards), there are no residue chemistry, occupational exposure, or toxicology issues that would preclude granting a conditional registration for the requested uses of saflufenacil on the requested crops. Registration should be made conditional pending the submission of an immunotoxicity study.

The proposed uses and the submitted data support: "Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of saflufenacil (2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide) and its metabolites *N*-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)-4-fluorobenzoyl]-*N'*-isopropylsulfamide and *N*-[4-chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea, calculated as the stoichiometric equivalent of saflufenacil, in or on the commodities."

Vegetable, legume, group 6	0.03 ppm
Vegetable, foliage of legume, group 7	0.10 ppm
Fruit, citrus, group 10	0.03 ppm
Fruit, pome, group 11	0.03 ppm
Fruit, stone, group 12	0.03 ppm
Nut, tree, group 14	0.03 ppm
Pistachio	0.03 ppm
Almond, hulls	0.10 ppm
Grain, cereal, group 15	0.03 ppm
Grain, cereal, forage, fodder and straw group 16	0.10 ppm
Cotton, undelinted seed	0.03 ppm

Cotton, gin byproducts	0.10 ppm
Sunflower, seed	1.0 ppm
Grape	0.03 ppm

The proposed uses and the submitted data also support: "Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only saflufenacil, 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide, in or on the commodities."

Milk	0.01 ppm
Cattle, meat	0.01 ppm
Cattle, fat	0.01 ppm
Cattle, liver	0.80 ppm
Cattle, meat byproducts, except liver	0.02 ppm
Goat, meat	0.01 ppm
Goat, fat	0.01 ppm
Goat, liver	0.80 ppm
Goat, meat byproducts, except liver	0.02 ppm
Hog, meat	0.01 ppm
Hog, fat	0.01 ppm
Hog, liver	0.80 ppm
Hog, meat byproducts, except liver	0.02 ppm
Sheep, meat	0.01 ppm
Sheep, fat	0.01 ppm
Sheep, liver	0.80 ppm
Sheep, meat byproducts, except liver	0.02 ppm
Horse, meat	0.01 ppm
Horse, fat	0.01 ppm
Horse, liver	0.80 ppm
Horse, meat byproducts, except liver	0.02 ppm

Data Gaps

Toxicology:

- As part of the new 40 CFR revised Part 158 requirement, an immunotoxicity study is required.

Chemistry:

860.1200 Directions for Use

- The BAS 800 04H FiRoCrop Herbicide contains directions for use on varieties of forage sorghum. However, forage sorghum is a member of the grass crop group, for which no data were submitted or tolerances proposed. The BAS 800 04H FiRoCrop Herbicide label should thus be amended to limit the sorghum use to sweet and grain varieties only.
- All of the sunflower field trials were performed with a water-dispersible granule (WG) formulation; whereas, the proposed use is for the suspension-concentrate (SC)

formulation. These formulation types are not considered to be equivalent for mid- to late-season foliar applications. The proposed sunflower use should thus be removed from the BAS 800 04H FiRoCrop Herbicide (SC) label and may be added to the BAS 800 01H TNV Herbicide (WG) label. Alternatively, bridging trials could be performed to determine the effect of the formulation type on residue levels.

860.1650 Submittal of Analytical Reference Standards

- Analytical standards of saflufenacil, M800H11, and M800H35 are currently available in the National Pesticide Standards Repository [Source: personal communication with T. Cole of the Analytical Chemistry Laboratory/Biological and Economics Analysis Division (ACL/BEAD), 1/15/09]. However, since the standards for M800H11 and M800H35 expired on 10/1/08, the petitioner is requested to provide a new supply to the Repository.

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F specifying the following:

- The tolerance expression for plant commodities should be revised to: "Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of saflufenacil (2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide) and its metabolites *N*-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3, 6-dihydro-1(2*H*)-pyrimidinyl)-4-fluorobenzoyl]-*N'*-isopropylsulfamide and *N*-[4-chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea, calculated as the stoichiometric equivalent of saflufenacil, in or on the commodities."

- The tolerance expression for livestock commodities should be revised to: "Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only saflufenacil, 2-chloro-5-[3, 6-dihydro-3-methyl-2, 6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide, in or on the commodities."

- Revised tolerance levels and commodity definitions are presented in Appendix C: Tolerance Summary Table.

Occupational and Residential Exposure:

- The RD should ensure that the personal-protective equipment (PPE) listed on the BAS 800 02H label is the correct PPE for this product.

- The RD should ensure that the restricted-entry intervals (REIs) listed on the BAS 800 02H and BAS 781 02H labels are correct for those two products.

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1.0 Executive Summary

Saflufenacil is a pre- and postemergence herbicide that acts by inhibiting protoporphyrinogen IX oxidase (protox inhibitor), which leads to chlorophyll destruction by photooxidation and causes bleaching of emerging foliar tissue. Protoporphyrinogen IX oxidase is one of the key enzymes in the porphyrin biosynthesis for the production of chlorophyll in plants and heme in mammals. It catalyzes the last common step in the biosynthesis of chlorophyll and heme. When protoporphyrinogen IX oxidase is inhibited in mammals, hemoglobin formation is reduced resulting in anemia. In addition, inhibition of the enzyme causes accumulation of different porphyrins and their precursors in various organs. As most uses of saflufenacil are preemergent at a maximum rate of 0.35 lb ai/acre, the potential for human exposure is minimal.

Toxicity/Hazard: Saflufenacil has low acute toxicity via the oral, dermal and inhalation routes of exposure (Toxicity Category III or IV). It is slightly irritating to the eye (Toxicity Category III). It is neither a dermal irritant nor sensitizer.

Short-term, subchronic, and chronic toxicity studies in rats, mice, and dogs identified the hematopoietic system as the target organ of saflufenacil. Protoporphyrinogen oxidase inhibition in the mammalian species may result in disruption of heme synthesis which in turn causes anemia. In these studies, decreased hematological parameters [red blood cells (RBC), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)] were seen at about the same dose level across species, except in the case of the dog, where the effects were seen at a slightly higher dose. These effects occurred around the same dose level from the short- through long-term exposures without increasing in severity. Effects were also seen in the liver (increased weight, centrilobular fatty change, lymphoid infiltrate) in mice, the spleen (increased spleen weight and extramedullary hematopoiesis) in rats, and in both these organs (increased iron storage in the liver and extramedullary hematopoiesis in the spleen) in dogs. These effects also occurred around the same dose level from the short- through long-term exposures without increasing in severity. No dermal toxicity was seen at the limit dose in a 28-day dermal-toxicity study in rats.

Carcinogenicity studies in rats and mice showed no evidence of increased incidence of tumors at the tested doses. Saflufenacil is weakly clastogenic in the *in vitro* chromosomal aberration assay in V79 cells in the presence of S9 activation; however, the response was not evident in the absence of S9 activation. It is neither mutagenic in bacterial cells nor clastogenic in rodents *in vivo*. Saflufenacil is classified as "not likely carcinogenic to humans."

Increased fetal susceptibility was observed in the developmental toxicity studies in the rat and rabbit and in the 2-generation reproduction study in the rat. Developmental effects such as decreased fetal body weights and increased skeletal variations occurred at doses that were not maternally toxic in the developmental study in rats, indicating increased quantitative susceptibility. In rabbits, developmental effects such as increased liver porphyrins were observed at doses that were not maternally toxic, indicating increased quantitative susceptibility. In the 2-generation reproduction study in rats, offspring effects such as increased number of stillborn pups, decreased viability and lactation indices, decreased pre-weaning body weight and/or body-weight gain, and changes in hematological parameters were observed at the maternally-toxic dose, indicating increased qualitative susceptibility.

In the acute neurotoxicity study, a decrease in motor activity was observed on the first day of dosing at the limit dose in males only. The finding was not accompanied by any other neuropathological changes and was considered a reflection of a mild and transient general systemic toxicity and not a substance-specific neurotoxic effect. In the subchronic neurotoxicity study, systemic toxicity (anemia) was seen at 1000 (66.2 mg/kg/day) and 1350 (101 mg/kg/day) ppm in males and females, respectively. There was no evidence of neurotoxicity or neuropathology in either study due to treatment.

Rat metabolism data indicate that saflufenacil is well absorbed and rapidly excreted. The maximum concentration of saflufenacil in blood and plasma was reached within 1 hour (h) of dosing and declined rapidly after 24 h. Excretion of orally dosed saflufenacil was essentially complete within 96 h, with the majority eliminated within the first 24 to 48 h. There was a sex-dependent difference in the excretion of orally administered saflufenacil. The main route of elimination in male rats was via the feces, while urinary excretion was the major route of elimination in females. The sex-dependent excretion was more pronounced at the low-dose level than at the high-dose level. Also, males had significantly higher biliary excretion of saflufenacil residues than females. Exhalation was not a relevant excretion pathway of saflufenacil. At 168 h after dosing, saflufenacil residues remaining in tissues were very low and occurred mainly in carcass, liver, skin, and gut contents.

The parent molecule and 3 major metabolites (M800H01, M800H03, M800H07) were identified and isolated from urine and feces. Minor metabolites that were identified include M800H05, M800H16, M800H17, M800H18, M800M19, and M800M20. There were no significant gender differences in metabolic profiles. Saflufenacil was metabolized by three major transformation steps, which were demethylation of the uracil ring system, degradation of the *N*-methyl-*N*-isopropyl group to NH_2, and cleavage of the uracil ring, forming a sulfonylamide group.

Dose-Response and Food Quality Protection Act (FQPA) Assessments: The saflufenacil risk assessment team recommends that the 10X FQPA safety factor (SF) for the protection of infants and children be reduced to 1X since there is an adequate toxicity database for saflufenacil and exposure data are complete or are estimated based on data that reasonably account for potential exposures. The recommendation is based on the following: 1) the established acute reference dose (aRfD, 5.0 mg/kg) and chronic RfD (cRfD, 0.046 mg/kg/day) are protective of any developmental and offspring effects. 2) There are no residual uncertainties concerning pre- and postnatal toxicity. 3) The changes in spleen (an organ of the immune system) weight observed only in rats at 32.3 mg/kg/day were attributable to increased clearance of defective RBCs (due to defective hemoglobin synthesis) and therefore not a specific immunotoxic effect. Therefore, based on the above consideration, HED does not believe that conducting a special series 870.7800 immunotoxicity study will result in a NOAEL less than the NOAEL of 4.6 mg//kg/day used to calculate the cRfD for saflufenacil and an additional uncertainty factor (UF_{DB}) for database uncertainties does not need to be applied. 4) There are no residual uncertainties with respect to exposure data. 5) The dietary food exposure assessment utilizes proposed tolerance-level residues and 100% crop treated (CT) information for all proposed commodities. By using this screening-level assessment, the acute and chronic exposures/risks will not be underestimated. 6) The dietary drinking water assessment utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations. 7) There are no registered or proposed uses of saflufenacil which would result in residential exposure. A 100-fold uncertainty factor (UF) (10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into

the acute and chronic RfD. The acute population-adjusted dose (aPAD) and the chronic PAD (cPAD) are equal to the acute and chronic RfDs, respectively, divided by the FQPA SF (1X). Saflufenacil is classified as "not likely carcinogenic to humans" by all relevant routes of exposure based on adequate studies in two animal species; therefore, cancer risk assessments are not required. In estimating margins of exposure (MOEs), the level of concern (LOC) is for MOEs $\leq$100 for the dermal and inhalation risk assessments. A 3% dermal-absorption factor and a 100% inhalation-absorption factor were used in the route-to-route extrapolation. The toxicological doses relevant to this assessment are summarized below.

acute dietary (general population, including infants and children)	no-observed adverse-effect level (NOAEL) = 500 mg/kg/day	acute RfD and aPAD = 5.0 mg/kg/day
chronic dietary	NOAEL = 4.6 mg/kg/day	chronic RfD and cPAD = 0.046 mg/kg/day
short-, intermediate-, and long-term dermal and inhalation	oral NOAEL = 5.0 mg/kg/day	LOC for MOEs <100 (occupational)

Note that while the new 40 CFR revised Part 158 requirement for an immunotoxicity study have not yet been fulfilled, the existing data are sufficient for endpoint selection for exposure/risk assessment scenarios and for evaluation of the requirements under FQPA. Further, the data requirements pertaining to this study (see Section 10.1) should be fulfilled as a condition of registration.

Dietary Risk Estimates (Food + Water): Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from the U.S. Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The acute and chronic analyses assumed 100% CT, DEEM™ 7.81 default processing factors, and tolerance-level residues for all foods. Drinking water was incorporated directly into the dietary assessment using the concentration for ground water generated by the Tier II Pesticide Root Zone Model Ground Water (PRZM GW). The resulting acute dietary (food + water) risk estimates using the DEEM-FCID™ model at the 95th percentile (<1% aPAD for all infants (<1 year old), the most highly-exposed population subgroup), are not of concern (<100% aPAD). The chronic dietary risk assessment shows that the chronic dietary risk estimates are not of concern (i.e., <100% cPAD). For the U.S. population, the exposure for food and water utilized 8.8% of the cPAD. The chronic dietary risk estimate for the highest exposed population subgroup, all infants (<1 year old), is 28% of the cPAD.

Residential Exposure: There are no residential uses proposed or currently registered for saflufenacil. Therefore, a residential risk assessment was not conducted.

Aggregate Risk: There are no uses of saflufenacil that are expected to result in residential exposures. Therefore, the aggregate exposure assessment takes into consideration dietary food + water exposure only. The acute and chronic dietary estimates represent acute and chronic aggregate risk, respectively.

Occupational Exposure/Risk to Mixer/Loaders and Applicators: Saflufenacil can be applied by aerial, chemigation, groundboom and rights-of-way equipment. In addition, applications can be made via dry bulk fertilizer. Based upon the proposed use pattern, HED expects handler exposure and risk from open mixing/loading liquids and dry flowables for aerial, chemigation, groundboom, and rights-of-way applications; impregnating liquids onto dry bulk fertilizer in

commercial and on-farm settings; applying sprays via aerial, groundboom, and rights-of-way applications; applying impregnated dry bulk fertilizer with commercial equipment or with grower-owned equipment; and open mixing/loading/applying via low-pressure handwand.

Handler exposure is expected to be short- or intermediate-term based on information provided on proposed labels. In addition, the short- and intermediate-term toxicological endpoints are the same; therefore, the estimates of risk for short-term duration exposures are protective of those for intermediate-term duration exposures. Long-term exposures are not expected; therefore, a long-term assessment was not conducted.

No chemical-specific data were available to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the Pesticide Handler's Exposure Database (PHED) Surrogate Exposure Guide (August, 1998). The saflufenacil product labels direct applicators and other handlers to wear: (1) BAS 800 01H TNV; BAS 800 04H FiRoCrop; BAS 804 00H LegVeg; BAS 781 02H: long-sleeve shirt, long pants, chemical-resistant gloves, shoes plus socks and protective eyewear and (2) BAS 800 02H: coveralls, short-sleeve shirt, short pants, chemical-resistant gloves, shoes plus socks, and protective eyewear. There are no data to assess impregnating liquids onto dry bulk fertilizer in commercial settings. The assumptions that the amount of saflufenacil handled per day in commercial settings (500–960 tons) make it unlikely that open mixing/loading is used. Therefore, as a reasonable surrogate for impregnation of dry bulk fertilizer in commercial settings, unit exposure values from PHED for engineering controls (closed mixing/loading) are used.

HED has determined that there are no risks of concern for occupational handlers associated with the use of saflufenacil, **provided workers wear protective gloves as recommended on the label. The RD should ensure that the PPE listed on the BAS 800 02H label (i.e., coveralls over short-sleeve shirt and short pants) is the correct PPE for that product.**

Occupational Post-application Risk: Most of the proposed uses for saflufenacil are soil-directed preplant or preemergent uses where no crop foliage is present. The proposed labels indicate that crop injury will result if the products are applied postemergent (over the top) to any crop. Currently, HED has no transfer coefficients or other data to assess postapplication dermal exposures to soil by occupational workers. In general, such exposures are considered to be negligible. Therefore, for the proposed soil-directed uses, postapplication dermal exposures and risks to occupational workers were not assessed. For the use on sunflowers as a dessicant, postapplication exposure is expected to be minimal since harvesting of sunflowers is typically done by machine.

The proposed labels have 12- and 24-hour REIs. The technical material has a Toxicity Category III for acute oral, acute dermal, and acute eye irritation. It has a Toxicity Category IV for acute inhalation and acute dermal irritation. Per the Worker Protection Standard (WPS), a 12-hour REI is required for chemicals classified under Toxicity Categories III and IV. Therefore, the REI of 12 hours appearing on the proposed saflufenacil labels are in compliance with the WPS. **The RD should ensure that the 24-hour REI appearing on the BAS 800 02H and BAS 781 02H labels is correct.**

Environmental Justice Considerations: Potential areas of environmental justice concerns, to the extent possible, were considered in this human-health risk assessment, in accordance with

U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under CSFII and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research: This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. The database listed below has been determined to require a review of its ethical conduct. It has received the appropriate review. It was concluded it does not violate current ethical standards.

Studies reviewed for ethical conduct: The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

Recommendation for Tolerances and Registration:

Pending submission of revised Sections B and F (see requirements under Directions for Use and Proposed Tolerances) and the submission of reference standards for the saflufenacil metabolites (see requirements under Submittal of Analytical Reference Standards), there are no residue chemistry, occupational exposure, or toxicology issues that would preclude granting a conditional registration for the requested uses of saflufenacil on the requested crops. Registration should be made conditional pending the submission of revised analytical enforcement methods (see requirements under Residue Analytical Methods) and an immunotoxicity study.

The proposed uses and the submitted data support: "Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of saflufenacil (2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide) and its metabolites *N*-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)-4-fluorobenzoyl]-*N'*-isopropylsulfamide and *N*-[4-chloro-2-fluoro-5-

({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea, calculated as the stoichiometric equivalent of saflufenacil, in or on the commodities."

Vegetable, legume, group 6	0.03 ppm
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Fruit, pome, group 11	0.03 ppm
Fruit, stone, group 12	0.03 ppm
Nut, tree, group 14	0.03 ppm
Pistachio	0.03 ppm
Almond, hulls	0.10 ppm
Grain, cereal, group 15	0.03 ppm
Grain, cereal, forage, fodder and straw group 16	0.10 ppm
Cotton, undelinted seed	0.03 ppm
Cotton, gin byproducts	0.10 ppm
Sunflower, seed	1.0 ppm
Grape	0.03 ppm

The proposed uses and the submitted data also support: "Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only saflufenacil, 2-chloro-5-[3, 6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide, in or on the commodities."

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Cattle, fat	0.01 ppm
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Goat, meat	0.01 ppm
Goat, fat	0.01 ppm
Goat, liver	0.80 ppm
Goat, meat byproducts, except liver	0.02 ppm
Hog, meat	0.01 ppm
Hog, fat	0.01 ppm
Hog, liver	0.80 ppm
Hog, meat byproducts, except liver	0.02 ppm
Sheep, meat	0.01 ppm
Sheep, fat	0.01 ppm
Sheep, liver	0.80 ppm
Sheep, meat byproducts, except liver	0.02 ppm
Horse, meat	0.01 ppm
Horse, fat	0.01 ppm
Horse, liver	0.80 ppm
Horse, meat byproducts, except liver	0.02 ppm

Data Gaps

See Section 10.0 for data needs and label recommendations.

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

BASF has submitted draft labels dated 1/31/08 for the 2.85 lb ai/gal SC formulation (BAS 800 04H FiRoCrop Herbicide; EPA Reg. 7969-ETI), for the 70% ai WG formulation (BAS 800 01H TNV Herbicide; EPA Reg. No. 7969-ETA), the 0.57 lb ai/gal EC formulation (BAS 781 02H Herbicide; EPA Reg. 7969-ETO), and the 17.8% WG formulation (BAS 804 00H LegVeg Herbicide; EPA Reg. 7969-EIN). Information pertaining to the proposed end-use products is listed in Table 2.1.1. A summary of the proposed use patterns on legume vegetables, citrus fruit, pome fruit, stone fruit, tree nuts, cereal grains, cotton, sunflowers, and grapes is detailed in Table 2.1.2.

Table 2.1.1. Summary of Proposed End-Use Products.

Trade Name	Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Label Date
BAS 800 04H FiRoCrop Herbicide	7969-ETI	29.74	SC	legume vegetables, cereal grains, cotton, sunflowers	Broadleaf weeds	Draft labels submitted 1/31/08
BAS 800 01H TNV	7969-ETA	70.0	WG	citrus fruit, pome fruit, stone fruit, tree nuts, grapes		
BAS 781 02H Herbicide	7969-ETO	6.24 + 55.04% dimethenamid	EC	corn, grain sorghum		
BAS 804 00H LegVeg Herbicide	7969-EIN	17.8 + 50.2% imazethapyr	WG	legume vegetables, corn		
BAS 800 02H Herbicide	7969-XXX	12.27%	EC	Christmas tree plantations, conifer and hardwood plantations, Noncropland areas[a]		

a. Includes: fence rows, non-irrigation ditch banks, petroleum-tank farms, pumping installations, railroad, rights-of-way (utility, pipeline, highway), storage areas, utility-plant sites and for establishment and maintenance of natural areas.

Table 2.1.2. Summary of Directions for Use of Saflufenacil.

Applic. Timing, Type, and Equip.	Formulation [EPA File Symbol]	App. rate (lb ai/acre)	Max. No. App. per Season	Max. Seasonal App. Rate (lb ai/acre)	PHI (days)	Use Directions and Limitations
Christmas-Tree Plantations, Conifer and Hardwood Plantations, Noncropland Areas						
Post, Directed to Ground	BAS 800 02H Herbicide 1 lb/gal EC [7969-XXX]	0.35	Not specified	0.35	Not specified	Applications are to be made in ≥10 gal/acre using aerial equipment and ≥20 gal/acre using ground equipment.
Corn, Sorghum, Small Grains						
Preplant/ Preemergent Broadcast, Ground or aerial	BAS 800 04H FiRoCrop Herbicide 2.85 lb/gal SC [7969-ETI]	0.0225-0.134	Not specified	0.134	80 (forage, silage)	Applications are to be made in ≥3 gal/acre using ground or aerial equipment.

Table 2.1.2. Summary of Directions for Use of Saflufenacil.

Applic. Timing, Type, and Equip.	Formulation [EPA File Symbol]	App. rate (lb ai/acre)	Max. No. App. per Season	Max. Seasonal App. Rate (lb ai/acre)	PHI (days)	Use Directions and Limitations
Legumes						
Preplant/ Preemergent Broadcast, Ground or aerial	BAS 800 04H FiRoCrop Herbicide 2.85 lb/gal SC [7969-ETI]	0.011-0.089	Not specified	0.089	Not specified	Applications are to be made in ≥3 gal/acre using ground or aerial equipment.
Cotton						
Preplant/ Preemergent Broadcast, Ground or aerial	BAS 800 04H FiRoCrop Herbicide 2.85 lb/gal SC [7969-ETI]	0.045	Not specified	0.045	Not specified	Applications are to be made in ≥3 gal/acre using ground or aerial equipment.
Citrus, Pome, & Stone Fruit; Tree Nuts						
Post, Directed to Orchard Floor	BAS 800 01H TNV Herbicide 30% WG [7969-ETA]	0.022-0.044	3	0.131	7 (nuts) 0 (fruit)	Applications are to be made in ≥10 gal/acre using ground equipment.
Grapes						
Post, Directed to Vineyard Floor	BAS 800 01H TNV Herbicide 30% WG [7969-ETA]	0.022	3	0.066	0	Applications are to be made in ≥10 gal/acre using ground equipment.
Sunflower						
Preharvest Dessication Broadcast, Ground or aerial	BAS 800 04H FiRoCrop Herbicide 2.85 lb/gal SC [7969-ETI]	0.0225-0.045	2	0.090	7	Applications are to be made in ≥3 gal/acre using ground or aerial equipment.

Note: Use of an adjuvant is required for burndown application to emerged weeds or sunflower.

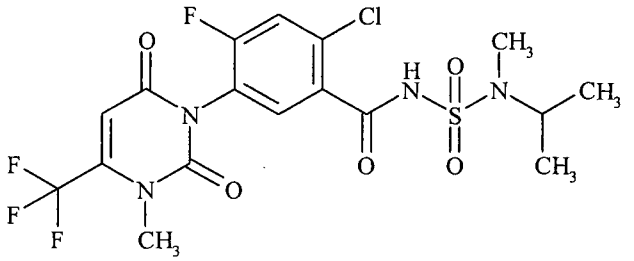
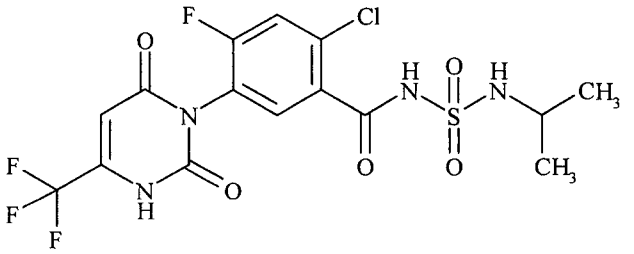
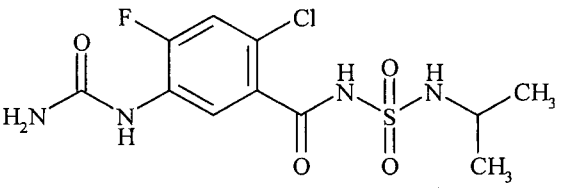
Table 2.1.3. Rotational Crop PBIs for Saflufenacil.

	PBI (months)					
	Application rate (lb ai/acre)					
Crop	0.0225	0.045	0.067	0.089	0.112	0.134
Corn	0	0	0	0	0	0
Sorghum	0	0	0	0	0	0
Small Grains	0	0	0	0	3	3
Chickpea Field Pea	0	0	3	3	6	6
Lentil	0	2	3	3	6	9
Soybean	1	2	4	4	6	6
Cotton	1	3	4	6	6	9
Other Crops	4	4	6	6	6	9

The submitted use directions for BAS 800 04H FiRoCrop Herbicide, BAS 800 01H TNV Herbicide, BAS 781 02H Herbicide, and BAS 804 00H LegVeg Herbicide are adequate to allow evaluation of the residue data relative to the proposed use. The BAS 800 04H FiRoCrop Herbicide contains directions for use on varieties of forage sorghum. However, forage sorghum is a member of the grass crop group, for which no data were submitted or tolerances proposed. The BAS 800 04H FiRoCrop Herbicide label should thus be amended to limit the sorghum use to

sweet and grain varieties only. Additionally, all of the sunflower field trials were performed with a WG formulation; whereas, the proposed use is for the SC formulation. These formulation types are not considered to be equivalent for mid- to late-season foliar applications. The proposed sunflower use should thus be removed from the BAS 800 04H FiRoCrop Herbicide (SC) label and added to the BAS 800 01H TNV Herbicide (WG) label. Alternatively, bridging trials could be performed to determine the effect of the formulation type on residue levels.

2.2 Structure and Nomenclature

TABLE 2.2. Saflufenacil and Metabolites Nomenclature.	
Chemical Structure	
Common name	Saflufenacil
Company experimental name	BAS 800 H (synonyms: AC 433 379, BASF Reg. No. 4054449)
IUPAC name	*N'*-[2-Chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)benzoyl]-*N*-isopropyl-*N*-methylsulfamide
CAS name	2-Chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide
CAS registry number	372137-35-4
End-use product (EP)	BAS 800 00H (70% WG formulation)
Chemical Structure	
Common name	M800H11
Chemical name	*N*-[2-Chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)-4-fluorobenzoyl]-*N'*-isopropylsulfamide
Chemical Structure	
Common name	M800H35
Chemical name	*N*-[4-Chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea

2.3 Physical and Chemical Properties

TABLE 2.3. Physicochemical Properties of Technical Grade Saflufenacil.	
Parameter	Value
Melting point	Average = 189.9°C, peak max = 193.4°C
pH	4.43 of 1% solution at 25°C
Bulk Density (ambient temp.)	0.661 kg/L (free fall), 0.736 kg/L (packed)
Water solubility (20°C)	in g/100-mL: 0.0025 in water (pH = 5); 0.0014 in pH 4 buffer; 0.21 in pH 7 buffer; not determined due to degradation in pH 9 buffer
Solvent solubility (20°C)	in g/100-mL: 19.4 acetonitrile; 24.4 dichloromethane; 55.4 *N,N*-dimethylformamide; 27.5 acetone; 6.55 ethyl acetate; 36.2 tetrahydrofuran; 35.0 butyrolactone; 2.98 methanol; 0.25 isopropyl alcohol; 0.23 toluene; <0.01 1-octanol; <0.005 n-heptane
Vapor pressure at 20/25°C	20°C = 4.5×10^{-15} Pa 25°C = 2.0×10^{-15} Pa
Dissociation constant (pK_a)	4.41
Octanol/water partition coefficient	Mean Log P_{ow} = 2.6 (P_{ow} = 368.3)
UV/visible absorption spectrum	wavelength maximum: λ_{max} = 271.6 nm extinction coefficient: ε = 9709 L/mol-cm

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Studies Available and Considered (animal, human, general literature)

Acute- oral, dermal, inhalation, eye irritation, skin irritation, dermal sensitization, neurotoxicity.
Subchronic- 21/28-day dermal toxicity in rat, oral 90-day rat, oral 90-day mouse, oral neurotoxicity rat.
Chronic- oral rat (combined chronic/carcinogenicity), oral carcinogenicity in mice and oral dog.
Reproductive/developmental- oral developmental rat and rabbit, rat reproduction/fertility.
Other- dermal-penetration study, mutagenicity studies (*in vitro* and *in vivo*), metabolism/pharmacokinetics studies, comparative bioavailability/toxicity, total porphyrin analysis mechanistic studies.

3.1.1.2 Mode-of-Action, Metabolism, Toxicokinetic Data

Saflufenacil is a pre- and postemergence herbicide that acts by inhibiting protoporphyrinogen IX oxidase (protox inhibitor), which leads to chlorophyll destruction by photooxidation and causes bleaching of emerging foliar tissue. Protoporphyrinogen IX oxidase is one of the key enzymes in the porphyrin biosynthesis for the production of chlorophyll in plants and heme in mammals. It catalyzes the last common step in the biosynthesis of chlorophyll and heme. When protoporphyrinogen IX oxidase is inhibited in mammals, hemoglobin formation is reduced resulting in anemia. In addition, inhibition of the enzyme causes accumulation of different porphyrins and their precursors in various organs.

Rat metabolism data indicate that saflufenacil is well absorbed and rapidly excreted. Regardless

of the dose administered, maximum concentration of saflufenacil in blood and plasma was reached within 1 hour of dosing and declined rapidly after 24 hours. Excretion of orally dosed saflufenacil was essentially complete within 96 hours, with the majority eliminated within the first 24 to 48 hours. The blood and plasma data demonstrated that the majority of the saflufenacil residues occurred in the plasma and were not bound to cellular elements of the blood. There was a sex-dependent difference in the excretion of orally administered saflufenacil. Following single low- and high-dose administration or a repeat high-dose administration, the main route of elimination in male rats was via the feces, whereas urinary excretion was the major route of elimination in females. The sex-dependent excretion was more pronounced at the low-dose level than at the high-dose level. The sex-dependent difference in excretion of orally dosed saflufenacil was also demonstrated by the biliary excretion data which showed significantly higher biliary excretion of saflufenacil residues in males than in females. Exhalation was not a relevant excretion pathway of saflufenacil. At 168 hours after dosing, saflufenacil residues remaining in tissues were very low and occurred mainly in carcass, liver, skin, and gut contents.

The parent molecule and 3 major metabolites (M800H01, M800H03, M800H07) were identified and isolated from urine and feces. Minor metabolites that were identified include M800H05, M800H16, M800H17, M800H18, M800M19, and M800M20. There were no significant gender differences in metabolic profiles. Saflufenacil was metabolized by three major transformation steps, which were demethylation of the uracil ring system, degradation of the *N*-methyl-*N*-isopropyl group to NH_2, and cleavage of the uracil ring, forming a sulfonylamide group.

3.1.1.3 Sufficiency of Studies/Data

The toxicity database is adequate for saflufenacil for the estimation of human-health risk and assessment of children's susceptibility, as required by FQPA. All studies evaluated were deemed acceptable and met guideline criteria with few exceptions; however, there was enough adequate information available for each study for toxicity characterization that this does not constitute a data gap.

3.1.2 Toxicological Effects

Saflufenacil has low acute toxicity via the oral, dermal and inhalation routes of exposure (Toxicity Category III or IV). It is slightly irritating to the eye (Toxicity Category III). It is neither a dermal irritant nor sensitizer.

Short-term, subchronic and chronic toxicity studies in rats, mice and dogs identified the hematopoietic system as the target organ of saflufenacil. Protoporphyrinogen oxidase inhibition in the mammalian species may result in disruption of heme synthesis which in turn causes anemia. In these studies, decreased hematological parameters [RBC, Ht, MCV, MCH, MCHC] were seen at about the same dose level [lowest-observed-adverse-effect levels (LOAELs) of 13 to 39 mg/kg/day] across species, except in the case of the dog, where the effects were seen at a slightly higher dose (LOAELs of 50 - 100 mg/kg/day). These effects occurred around the same dose level from short- through long-term exposures without increasing in severity. Effects were also seen in the liver (increased weight, centrilobular fatty change, lymphoid infiltrate) in mice, the spleen (increased spleen weight and extramedullary hematopoiesis) in rats, and in both these organs (increased iron storage in the liver and extramedullary hematopoiesis in the spleen) in dogs. These effects also occurred around the same dose level from short- through long-term exposures without increasing in severity. No dermal toxicity was seen at the limit dose (1000

mg/kg/day) in a 28-day dermal-toxicity study in rats.

Carcinogenicity studies in rats and mice showed no evidence of increased incidence of tumors at the tested doses. Saflufenacil is weakly clastogenic in the *in vitro* chromosomal aberration assay in V79 cells in the presence of S9 activation; however, the response was not evident in the absence of S9 activation. It is neither mutagenic in bacterial cells nor clastogenic in rodents *in vivo*. Saflufenacil is classified as "not likely carcinogenic to humans."

Increased fetal susceptibility was observed in the developmental toxicity studies in the rat and rabbit and in the 2-generation reproduction study in the rat. Developmental effects such as decreased fetal body weights and increased skeletal variations occurred at doses (20 mg/kg/d) that were not maternally toxic in the developmental study in rats, indicating increased quantitative susceptibility. In rabbits, developmental effects such as increased liver porphyrins were observed at doses (200 mg/kg/d) that were not maternally toxic, indicating increased quantitative susceptibility. In the 2-generation reproduction study in rats, offspring effects such as increased number of stillborn pups, decreased viability and lactation indices, decreased pre-weaning body weight and/or body-weight gain, and changes in hematological parameters were observed at the maternally-toxic dose of 50 mg/kg/d (decreased food intake, body weight, body-weight gain, and changes in hematological parameters and organ weights indicative of anemia), indicating increased qualitative susceptibility.

In the acute neurotoxicity study a decrease in motor activity was observed on the first day of dosing at the limit dose (2000 mg/kg/d) in males only. The finding was not accompanied by any other neuropathological changes and was considered a reflection of a mild and transient general systemic toxicity and not a substance-specific neurotoxic effect. In the subchronic neurotoxicity study, systemic toxicity (anemia) was seen at 1000 (66.2 mg/kg/day) and 1350 (101 mg/kg/day) ppm in males and females, respectively. There was no evidence of neurotoxicity or neuropathology in either study due to treatment.

3.1.3 Dose-Response Assessment

Saflufenacil has low acute toxicity. The hematopoietic system was the target organ in mice, rats, and dogs. These effects occurred at comparable dose levels in all species tested (except for dogs) from the short- through long-term exposures without increasing in severity. Effects were also seen in the liver in mice, the spleen in rats, and in both of these organs in dogs. These effects also occurred around the same dose level from the short- through long-term exposures without increasing in severity. Although a decrease in motor activity was observed at the limit dose (2000 mg/kg/day) after a single exposure, this effect was not considered evidence for neurotoxicity but rather indicative of general malaise as it was not corroborated by the subchronic neurotoxicity study and no indication of neurotoxicity was seen in any other study in the database. There is evidence of increased susceptibility following pre-natal exposures to rats and rabbits and pre- and post-natal exposure to rats. There is no evidence of carcinogenicity and there are no mutagenic concerns. No dermal or systemic toxicity was seen following repeated dermal applications at the limit dose. The most sensitive endpoints established in the most sensitive species are selected for assessing risks from dietary and occupational exposures to saflufenacil. The conventional interspecies extrapolation (10X) and intraspecies variation (10X) UFs were applied for all exposure scenarios. The FQPA SF was not needed (i.e., 1X) since there are no residual concerns for pre-and or post-natal toxicity or exposure data.

Note that while the new 40 CFR revised Part 158 requirement for an immunotoxicity study has not yet been fulfilled, the existing data are sufficient for endpoint selection for exposure/risk assessment scenarios and for evaluation of the requirements under FQPA. Further, the data requirements pertaining to immunotoxicity (see Section 10.1) should be fulfilled as a condition of registration.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

The absorption and metabolism of saflufenacil was investigated with a single oral administration at 5 mg/kg or 1000 mg/kg (^{14}C-saflufenacil) and with repeated dosing (14 oral applications with unlabelled saflufenacil at 100 mg/kg bw and one oral application with labeled ^{14}C-saflufenacil at 100 mg/kg bw). Saflufenacil was rapidly absorbed, metabolized, and excreted. Regardless of the dose administered, maximum concentration of saflufenacil in blood and plasma was reached within 1 hour of dosing and declined rapidly after 24 hours. Excretion of orally dosed saflufenacil was essentially complete within 96 hours, the majority was eliminated within the first 24 to 48 hours. The blood and plasma data demonstrated that the majority of the saflufenacil residues occurred in the plasma and were not bound to cellular elements of the blood. The primary routes of elimination were the urine in females and the feces in males. After a single oral administration of 100 mg/kg bw of ^{14}C-saflufenacil following 168 hours, the total amounts of radioactivity excreted in urine were 52.6 and 86.6% in males and females, respectively. In feces, 43.3 and 9.8% of administered radioactivity (AR) were recovered in males and females, respectively. With repeat dosing, a similar pattern of excretion was also seen. After 168 hours, the total amounts of radioactivity excreted in urine were 67.8 and 83.4% in males and females, respectively. In feces, 35.8 and 13.4% of AR were recovered in males and females, respectively. After a single oral administration of 5 mg/kg bw within 168 hours, 26.0 and 96.1% of AR were excreted in urine of male and female rats, respectively. In feces, 81.2 and 12.8% AR were recovered in males and females, respectively. This result demonstrated a sex-specific excretion pattern for ^{14}C-saflufenacil with a higher amount of urinary excretion for females than for males. This sex difference was more pronounced at the low-dose level than at the high-dose level.

Males had up to three-fold higher internal exposures than females. The area under the curve (AUC) values for doses of ^{14}C-saflufenacil of 4, 20, and 100 mg/kg bw were 741, 2131, 4502 [µg Eq × h/g] for males and 247, 754, and 3057 [µg Eq × h/g] for females. Increasing the dose by a factor of 25 resulted in an increase of the AUC-values by a factor of 6.1 in males and 12.4 in females.

After a single oral dose of ^{14}C-saflufenacil at 5 or 100 mg/kg bw, analyses of radioactivity in tissues indicated higher levels in males than in females at respective time points and dose levels; whereas, the pattern of distribution in the various organs and tissues was similar in both sexes. Tissue radioactivity concentrations generally declined with time parallel to plasma concentrations. Throughout the time course of the experiments, highest radioactivity levels were generally found in the gastrointestinal (GI) tract, liver, kidneys, lungs, and thyroid; whereas, radioactivity levels were lowest in brain and bone. Similar findings were noted with repeat dosing. There was no evidence of bioaccumulation.

Higher biliary excretion was noted in males when compared to females. Within 48 hours of administration of ^{14}C-saflufenacil, excretion of radioactivity in the bile in males and females was 52.3 and 18.9% and 67.8 and 35.5% AR at 5 and 100 mg/kg bw dose levels, respectively.

Executive summaries for each of these studies are provided in Appendix A.3.

3.3.2 Evidence of Neurotoxicity

There was no evidence of neurotoxicity or neuropathology in the acute and subchronic neurotoxicity studies. In the acute neurotoxicity study a decrease in motor activity was observed on the first day of dosing at the limit dose (2000 mg/kg/day) in males only. The finding was not accompanied by any other neuropathological changes and was considered a reflection of a mild and transient general systemic toxicity and not a substance-specific neurotoxic effect. Additionally, it was not corroborated in the subchronic neurotoxicity study, there was no other indication of neurotoxicity in any study in the database, and it was not consistent with the known mammalian mode of action for this chemical. In the subchronic neurotoxicity study, systemic toxicity was seen at 1000 (66.2 mg/kg/day) and 1350 (101 mg/kg/day) ppm in males and females, respectively.

3.3.3 Additional Information from Literature Sources

The literature search did not reveal relevant information.

3.3.4 Pre-and/or Postnatal Toxicity

3.3.4.1 Determination of Susceptibility

There is evidence of increased susceptibility in rabbit and rat fetuses to *in utero* and post-natal exposure to saflufenacil. In a developmental toxicity study in rabbits, increased liver porphyrins were observed at a dose (200 mg/kg/day) lower than that which caused maternal toxicity (600 mg/kg/day, increased necropsy findings, triglycerides, and total liver porphyrins). In a rat developmental toxicity study, decreased fetal body weights and increased skeletal variations occurred at a dose (20 mg/kg/day) lower than the dose (60 mg/kg/day) that caused maternal toxicity (decrease hemoglobin, Ht, MCV, and MCH). In the 2-generation reproduction study in rats, offspring effects such as increased number of stillborn pups, decreased viability and lactation indices, decreased pre-weaning body weight and/or body-weight gain, and changes in hematological parameters were observed at the maternally-toxic dose of 50 mg/kg/day (decreased food intake, body weight, body-weight gain, and changes in hematological parameters and organ weights indicative of anemia).

3.3.4.2 Degree-of-Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

Since there is quantitative and qualitative evidences of increased susceptibility of the young following exposure to saflufenacil pre-and post natal exposures, a degree-of-concern analysis was performed to: A) determine the LOC for the effects observed when considered in the context of all available toxicity data; and B) identify any residual uncertainties after establishing toxicity endpoints and traditional UFs to be used in the risk assessment of this chemical. The LOC is low for the increased susceptibility since: 1) clear NOAELs/LOAELs were established for the developmental effects seen in rats and rabbits as well as for the offspring effects seen in the two-generation reproduction study; 2) none of the effects in the developmental or reproduction studies were attributable to a single exposure; 3) dose-response relationship for the effects of concern are well characterized; 4) the effects of concern are used for assessing dermal

and inhalation risks; 5) the dose used for chronic dietary risks would be protective of the developmental and offspring effects; and 6) there are no residential uses. Therefore, there are no residual uncertainties for pre-and/or post-natal susceptibility.

3.3.5 Recommendation for a Developmental Neurotoxicity Study

Although a decrease in motor activity observed in males only was seen at the limit dose in an acute neurotoxicity study, this effect was not considered to be indicative of neurotoxicity but rather of general malaise. This conclusion is based on the observation that the effects were not corroborated in the subchronic neurotoxicity study and no clinical signs indicative of neurotoxicity or neuropathology were seen in the acute or subchronic neurotoxicity study or in any of the other subchronic or chronic studies. No central nervous system malformations were seen in the pre-natal developmental toxicity studies. Therefore, a DNT is not required.

3.4 FQPA SF for Infants and Children

There is evidence for increased susceptibility following pre-and or post-natal exposures. However, the LOC is low for the increased susceptibility since clear NOAELs/LOAELs were established for the developmental effects seen in rats and rabbits as well as for the offspring effects seen in the two-generation reproduction study; a dose-response relationship for the effects of concern are well characterized; the effects of concern are used for assessing dermal and inhalation risks; and the dose used for overall risk assessments would be protective of the developmental and offspring effects. Therefore, there are no residual uncertainties for pre-and/or post-natal susceptibility.

The increase in spleen weight seen only in rats at 32.3 mg/kg/day is attributable to an increased clearance of defective RBCs (i.e, defective hemoglobin synthesis) and is thus an indication of toxicity to the hematopoietic system rather than to the immune system. In addition, the overall weight of evidence suggests that this chemical does not directly target the immune system. Therefore, HED does not believe that conducting a special series 870.7800 immunotoxicity study will result in a point of departure (PoD) lower than the PoD (approximately 5 mg/kg/d) used for overall risk assessment. Consequently, a database UF is not need for the lack of this study.

There are also no additional residual uncertainties with respect to exposure data. The dietary food exposure assessment utilizes recommended tolerance-level residues and 100% CT information for all commodities. By using these screening-level assessments, acute and chronic exposures/risks will not be underestimated. The dietary drinking water assessment utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations. There is no potential for residential exposure.

Based on the hazard and exposure considerations, the default FQPA SF is not needed (i.e, 1X) for this risk assessment.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 aRfD - General Population (including females age 13-49)

Study Selected: Acute Neurotoxicity Study (ACN)/Rat

MRID No.: 47128127
Executive Summary: See Appendix A, Guideline [§ 870.6200a]

Dose and Endpoint for Establishing aRfD: The systemic NOAEL for males is 500 mg/kg bw. A systemic LOAEL is 2000 mg/kg bw (males) based on the decreased motor activity representing mild and transient systemic toxicity. A systemic LOAEL was not established for females.

Comments on Study/Endpoint/UFs: The acute neurotoxicity study was selected because the endpoint chosen, decreased motor activity occurred following a single exposure. However, the decrease in motor activity was not viewed as an acute neurotoxic effect because it was transient and likely due to general malaise, the effect was not corroborated in the subchronic neurotoxicity study, there was no other indication of neurotoxicity in any other study in the database, and it is not consistent with the known mammalian mode of action for this chemical. An UF of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation (10X).

$$\textbf{aRfD} = \frac{\text{500 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{5.0 mg/kg/day}$$

3.5.2 aRfD - Females age 13-49 years old

Comments on Study/Endpoint/UFs: An aRfD for females 13-49 is not warranted because the effects (skeletal variations such as misshapen bones, delays in ossification, and wavy ribs) observed in the developmental study in the rat is not a result of a single dose. The skeletal variations are the result of bone deposition which does not occur during a single day. The process of bone deposition begins with cartilage deposition followed by calcification. Unlike supernumerary ribs or missing bones, which may be caused by the activation or inactivation of genes and could be the outcome of a single exposure, the process of bone deposition occurs over several days and is, therefore, not considered appropriate for establishing an aRfD.

3.5.3 cRfD

Study Selected: Chronic Toxicity/Carcinogenicity (Feeding)/Mouse

MRID No.: 47128119
Executive Summary: See Appendix A, Guideline [§ 870.4300]

Dose and Endpoint for Establishing cRfD: The NOAEL of 4.6 mg/kg/day is based on minimally decreased (3-5%) red blood cells, hemoglobin, and Ht and porphyria observed in the satellite group (sacrificed at 10 months) in the males at 13.8 mg/kg/day (LOAEL).

UF(s): An UF of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation (10X).

Comments about Study/Endpoint/UF: This study provides the lowest NOAEL in the database (most sensitive endpoint) and will also provide the most protective limits for human effects.

$$\textbf{cRfD} = \frac{\text{4.6 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.046 mg/kg/day}$$

3.5.4 Dermal Absorption

Study Selected: Dermal Penetration Study/Rat

MRID No.: 47128214
Executive Summary: See Appendix A, Guideline [§ 870.7600]

Based on the dermal penetration study in rats following 10 hours of exposure, a dermal-absorption factor of 3% is appropriate for human risk assessment.

3.5.5 Dermal and Inhalation Exposure (Short-, Intermediate-, and Long-Term)

Short-, Intermediate-, and Long-Term Dermal and Inhalation Exposures

Study Selected: Developmental Toxicity Study in the Rat

MRID No.: 47128115
Executive Summary: See Appendix A, Guideline [§ 870.3100]

Dose and Endpoint for Establishing MOEs: The NOAEL is 5 mg/kg bw/d, based on decreased fetal weights and increased skeletal variations 20 mg/kg/day (LOAEL).

Comments on Study/Endpoint/UFs: This endpoint was chosen because it was appropriate for the duration of exposure and the population of concern. An UF of 100 was applied to account for inter species extrapolation (10X) and intraspecies variation (10X). The LOC for the MOE is <100. The dermal-absorption factor is 3%, based on a dermal penetration study in rats. HED assumes equivalent toxicity via the inhalation route.

3.5.6 Levels of Concern for Margin of Exposure

Table 3.5.7. Summary of LOCs for Risk Assessment.

Route	Short-Term (1-30 Days)	Intermediate-Term (1-6 Months)	Long-Term (>6 Months)
Occupational (Worker) Exposure			
Dermal	100[a]	100	100
Inhalation	100	100	100

[a] LOC = interspecies extrapolation (10X), intraspecies variation (10X) UFs.

3.5.7 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. However, an aggregated exposure risk assessment incorporating residential exposures is not required since there are no residential uses for saflufenacil at this time.

For oral exposure, dietary exposure and water were aggregated. For occupational exposure dermal and inhalation exposure were combined since the effects of concern are the same and identified from the same study.

3.5.8 Classification of Carcinogenic Potential

Saflufenacil is classified as "not likely carcinogenic to humans" based on the absence of an increased incidence of tumors in the mouse and rat carcinogenicity studies and the lack of mutagenicity. Therefore, cancer risk is not of concern for this chemical.

3.5.9 Summary of Toxicological Doses and Endpoints for saflufenacil for Use in Human-Health Risk Assessments

Table 3.5.9a. Summary of Toxicological Doses and Endpoints for Saflufenacil for Use in Dietary Human-Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA SFs	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)[1]	NOAEL = 500 mg/kg bw	UF_A = 10X UF_H = 10X FQPA SF = 1X	**Acute RfD** = 5.0 mg/kg aPAD = 5.0 mg/kg	Acute Neurotoxicity Study NOAEL = 500 (M) and 2000 (F) mg/kg bw. LOAEL was 2000 mg/kg bw (males) based on the decreased motor activity representing mild and transient systemic toxicity. LOAEL was not established for females.
Chronic Dietary (All Populations)[2]	NOAEL = 4.6 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	**Chronic RfD** = 0.046 mg/kg/day **cPAD** = 0.046 mg/kg/day	Chronic/Carcinogenicity (mouse) NOAEL = 4.6 mg/kg bw/d (males) and 18.9 mg/kg bw/d (females). LOAELs = 13.8 mg/kg bw/d (males) and 38.1 mg/kg bw/day (females) based on decreased red blood cells, hemoglobin, and Ht and porphyria observed in the satellite group.
Cancer (oral, dermal, inhalation)	Classification: Not likely carcinogenic to humans based on the lack of tumors in the mouse and rat carcinogenicity studies and lack of mutagenicity.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose.

1 Not harmonized with Canada and Australia

2 Harmonized with Canada and Australia

Table 3.5.9b. Summary of Toxicological Doses and Endpoints for saflufenacil for Use in Occupational Human-Health Risk Assessments.

Exposure/ Scenario	Point of Departure	UFs	LOC for Risk Assessment	Study and Toxicological Effects
Dermal Short-Intermediate- and long- Term (1-30 days, 1-6 months, and >6 months, respectively)	NOAEL 5 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X Dermal absorption factor = 3%	Occupational LOC for MOE = 100	Developmental study -Rat NOAEL = 5 mg/kg bw/d. LOAEL= 20 mg/kg bw/d (males) based on decreased fetal bodyweight and increased skeletal variations.
Inhalation Short-Intermediate- and long- Term (1-30 days, 1-6 months, and >6 months, respectively)	NOAEL 5 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X Inhalation-absorption rate = 100%	Occupational LOC for MOE = 100	Developmental study -Rat NOAEL = 5 mg/kg bw/d. LOAEL= 20 mg/kg bw/d (males) based on decreased fetal bodyweight and increased skeletal variations.
Cancer (oral, dermal, inhalation)	Classification: Classification: Not likely carcinogenic to humans based on the lack of tumors in the mouse and rat carcinogenicity studies and lack of mutagenicity.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. MOE = margin of exposure. LOC = level of concern.

3.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, saflufenacil may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

No public health/epidemiology data were used in developing this risk assessment. Since saflufenacil is a new chemical, data are not available.

5.0 Dietary Exposure/Risk Characterization

The following references apply to this section:
Residue Chemistry Summary - D349938, G. Kramer, pending
Dietary Exposure - D364183, G. Kramer, pending
Drinking Water Degradates Identification - D356619, G. Orrick, 01-DEC-2008
Estimated Drinking Water Concentrations - D349860, G. Orrick, 15-APR-2009

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The nature of the residue in plants (resulting from preplant/preemergence application) is adequately understood based on acceptable metabolism studies conducted on corn, soybean, and tomato in conjunction with the confined rotational crop study (see Table B.1.1 for structures of metabolites). A waiver request for a sunflower (postemergence) metabolism study was approved. In plants, the main reactions involved in the metabolic pathway of saflufenacil are *N*-demethylation at the uracil ring to form M800H02, stepwise degradation (*N*-dealkylation) of the *N*-methyl-*N*-isopropyl group to form M800H05, hydrolytic cleavage of the uracil ring generating a urea side chain, and hydroxylation of the phenyl ring. M800H11 was found in all corn and soybean matrices from both ^{14}C-labeled uracil and ^{14}C-labeled phenyl saflufenacil. M800H11 is formed when saflufenacil undergoes demethylation at both nitrogen atoms. M800H35 was detected only after ^{14}C-labeled phenyl saflufenacil treatment and was detected at higher levels in soybean matrices. M800H35 is formed when parent saflufenacil undergoes demethylation at the sulfonylurea side chain and cleavage of the uracil ring. The major residue identified with the uracil-label studies was trifluoroacetic acid (TFA) (see Appendix B: Metabolism Assessment, Table B.1.1).

5.1.2 Metabolism in Rotational Crops

The metabolism of saflufenacil in rotational crops appears to be consistent with the pathway observed in the plant metabolism studies. Unless the petitioner requests plantback intervals (PBIs) shorter than 4 months, no additional data are required, and tolerances for inadvertent residues in/on rotational crops need not be established in conjunction with the currently proposed uses.

5.1.3 Metabolism in Livestock

The nature of the residue in livestock is adequately understood based on acceptable metabolism studies conducted on lactating goats and laying hens. Saflufenacil was metabolized by several dealkylation steps occurring at two different sites in the molecule (*N*-isopropyl-*N*-methylsulfamide side chain and at the uracil ring) and via hydrolytic opening of the uracil ring (goat only). In the ruminant metabolism study, saflufenacil was a major residue in all matrices.

M800H04, a ring opening product, was the only significant metabolite (>10% total radioactive residue, TRR) found (liver). In the poultry metabolism study, saflufenacil was a major residue in all matrices and no significant metabolites were found.

FIGURE 2. Proposed Metabolic Profile of saflufenacil in Soybean.

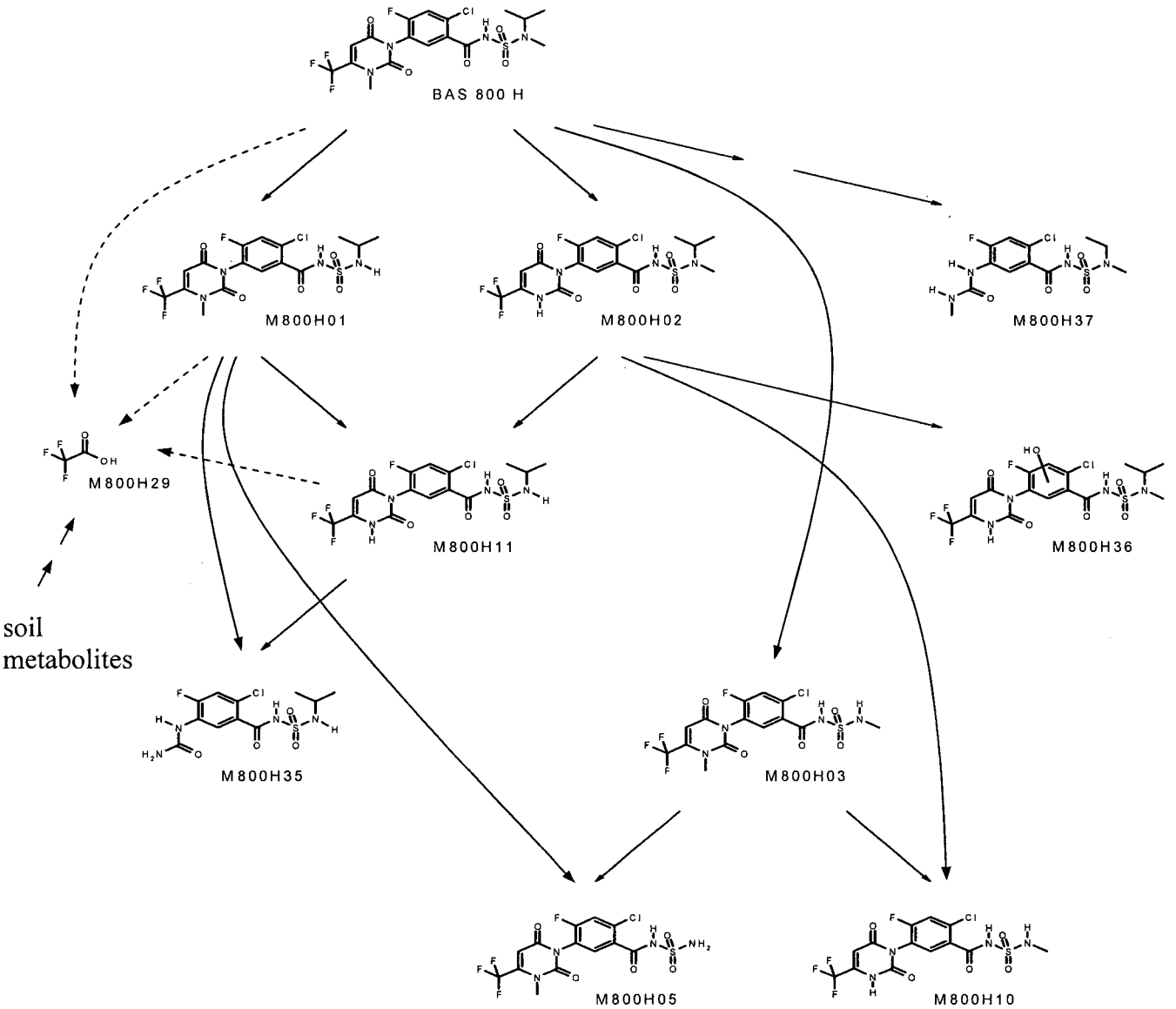


Figure 2 is reproduced from the study report. BAS 800 H = saflufenacil.

5.1.4 Analytical Methodology

The petitioner has submitted two liquid chromatography/mass spectroscopy/mass spectroscopy (LC-MS/MS) analytical methods for the determination of residues of the parent and its metabolites in/on plant and livestock commodities. BASF Method D0603/02 was developed for determination of residues of saflufenacil and its metabolites M800H11 and M800H35 in different plant matrices using LC-MS/MS. The limit of quantitation (LOQ) was 0.01 ppm for each analyte in food matrices and 0.025 ppm for each analyte in feed matrices. BASF analytical Method No. L0073/01 was developed for determination of saflufenacil in livestock matrices using LC-MS/MS. The LOQ was 0.01 ppm in all matrices. These methods were used as the

data-collection methods in the analysis of samples for residues of concern from the various studies associated with the current petition. Each method has been adequately validated by the petitioner as well as by independent laboratories. Method No. L0073/01 was also adequately radiovalidated using weathered samples obtained from metabolism studies.

HED has determined that Methods D0603/02 and L0073/01 are suitable enforcement methods for plant and livestock commodities, respectively, as defined in Standard Operating Procedure (SOP) No. ACB-019 (9/15/08).

5.1.5 Environmental Degradation

Saflufenacil is slowly photolyzed in water (half-life of 57 days at pH 5) and on soil (half-lives of 83 and 87 days) at 22°C. Also, the compound is relatively stable to hydrolysis at pH 5, almost stable at pH 7 (half-life of 248 days), and readily hydrolyzed at pH 9 (half-life of 4.9 days). Therefore, alkaline hydrolysis is a major degradation route for saflufenacil in high pH environments.

Saflufenacil biodegrades in 1 to 5 weeks in aerobic soil (half-lives of 8.5-34 days) and less quickly in aerobic aquatic environments of pH 5.6 to 6.4 (half-lives of 50 and 107 days). Therefore, aerobic soil metabolism is another major degradation route for saflufenacil that will operate in the environment at any pH value.

Biodegradation in anaerobic aquatic environments is uncertain, as the submitted anaerobic aquatic metabolism study systems were aerobically stratified, with anaerobic sediments and aerobic water columns. Half-lives were 28 and 29 days, which is less than those for the submitted aerobic aquatic metabolism study. However, system pH values ranged from 5.5 to 8.5, indicating that alkaline hydrolysis may have appreciably contributed to degradation. An anaerobic soil metabolism study is in development and has not been submitted at the time of writing.

Dissipation occurred with half-lives of 2.4 to 22 days in terrestrial field dissipation studies conducted in the continental U.S., which is consistent with the submitted, laboratory-derived data. Dissipation was slower in Canadian field plots (half-lives of 25 days and >>20 days).

Major degradates that are structurally similar to the parent compound include M01, M02, M04, M07, M08, M15, M22, and the soil photolysis product number 8. Major cleavage products of saflufenacil include M26, trifluoroacetic acid, M31, M33, and TFP. Another major aqueous photolysis product was isolated as well (unknown 3/4/7/6), but not identified. Major degradates that did not decline in amount in unsterile study conditions include M7, M29, and product 8 (see Appendix B: Metabolism Assessment, Table B.1.2).

5.1.6 Comparative Metabolic Profile

The primary routes of metabolism in animals and plants and degradation in the environment were basically the same: *N*-demethylation at the uracil ring, stepwise degradation (*N*-dealkylation) of the *N*-methyl-*N*-isopropyl group, and hydrolytic cleavage of the uracil ring. Unique environmental pathways included the addition of hydrogen to the double bond in the uracil ring and the formation of trifluoroacetic acid.

5.1.7 Toxicity Profile of Major Metabolites and Degradates

Toxicity data was not submitted for the metabolite TFA. However, the Residue of Concern Knowledgebase Subcommittee (ROCKS) concluded that "TFA is not likely to contribute to the toxic effects found for saflufenacil. Exposure to TFA from saflufenacil use would be insignificant compared to other pesticides" (ROCKS Decision Memo, B. Daiss, 1/6/09; D359645). Additionally, TFA was observed at <0.2 ppm; HED does not consider this residue to be of concern at the levels observed (D325826, Rate, D., 25-SEPT-2007). Data are not available for the other metabolites of saflufenacil.

5.1.8 Pesticide Metabolites and Degradates of Concern

Table 5.1.8. Summary of Metabolites and Degradates to be Included in the Risk Assessment.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crops	Saflufenacil + M800H11, M800H35	Saflufenacil + M800H11, M800H35
	Rotational Crops	Saflufenacil + M800H11, M800H35	Not Applicable
Livestock	Ruminants	Saflufenacil	Saflufenacil
	Poultry		
Drinking Water		Saflufenacil + M800H01, M800H02, M800H07, M800H08, M800H15, M800H22, Product 8	Not Applicable

Plants: The HED ROCKS determined that residues of concern for the tolerance expression and risk assessment consist of saflufenacil, M800H11, and M800H35 (Memo, B. Daiss, 1/6/09; D359645). This conclusion applies only to preplant/preemergence and sunflower harvest-aid uses. M800H11 is a major metabolite (>10% TRR) found in all corn and soybean matrices from both uracil and phenyl radiolabeled saflufenacil. It has the same basic structure as the parent, with demethylation at both nitrogen atoms. While the M800H35 metabolite is generally found in smaller quantities than M800H11, it is significant in soybean matrices and rotational crops. M800H35 is also structurally similar to saflufenacil, with cleavage of the uracil ring. In addition, the petitioner proposed that the residue definition include both M800H11 and M800H35 and has provided field residue data and an analytical enforcement method for both metabolites. M800H11 and M800H35 should be considered as toxicologically equivalent to saflufenacil due to their structural similarity. Even though M800H11 and M800H35 are not major residues in human food commodities, their inclusion in the tolerance expression is necessary to facilitate monitoring in livestock feed commodities.

TFA was detected at relatively high levels in all matrices from ^{14}C-labeled phenyl saflufenacil treatment. The saflufenacil team did not propose to include TFA as a residue of concern because 1) it is not structurally similar to the parent compound, 2) the toxicity of TFA is due to its strong acidity (pKa<1). At neutral pH, TFA would exist as an anion and not the acid and would therefore not exhibit acid toxicity (http://www.afeas.org/environ.html), and 3) it is not likely to contribute to toxic effects found for saflufenacil.

Livestock: The ROCKS determined that saflufenacil *per se* is the only residue of concern in livestock for the tolerance expression and risk assessment (Memo, B. Daiss, 1/6/09; D359645). Saflufenacil was the only major residue in all matrices in both the ruminant and poultry studies.

ROCKS noted that livestock may be exposed to M800H11 and M800H35 through the diet. However, since saflufenacil is an early-season herbicide, there is low potential for dietary exposure to M800H11 and M800H35 in livestock. Therefore, the parent is the only residue of concern for the currently proposed uses.

Water: The ROCKS determined that residues of concern for the risk assessment consist of saflufenacil, M800H01, M800H02, M800H07, M800H08, M800H15, M800H22, and Product 8 (Memo, B. Daiss, 1/6/09; D359645). Environmental fate studies indicate that metabolites M800H01, M800H02, M800H07, M800H08, and M800H22 are major, nontransient degradates in aerobic soil. They are mobile in soil and can therefore be expected to occur in surface water runoff and/or in ground water leachate. Product 8 is seen only in soil photolysis studies but was increasing in concentration at the end of the study so should be included as a metabolite of concern. M800H15 is detected in anaerobic environments only. However since it is mobile and likely to leach, it is a potential concern for groundwater. Metabolites M800H01, M800H02, M800H08, and Product 8 have the same basic structure as the parent – with the uracil ring intact. Metabolites M800H07, M800H15 and M800H22 are also structurally similar to the parent but with cleavage of the uracil ring.

Metabolite M800H04 is structurally similar to the parent compound and was identified as a major hydrolysis degradate. However, M800H04 is not of exposure concern because it was seen in the hydrolysis study only at pH 9 and it is transient.

Additional major degradates identified in the environmental fate studies are the cleavage products M800H26, M800H29, M800H31, M800H33, and TFP. M800H26 and M800H33 are found at relatively low levels in aerobic soil. M800H26 is transient. In general, these cleavage products are not expected to contribute significantly to risk relative to the metabolites that are structurally similar to the parent and are therefore not considered metabolites of concern.

The metabolites of concern for drinking water are assumed to have equivalent toxicity to the parent due to their structural similarity.

5.1.9 Drinking Water Residue Profile

The Estimated Drinking Water Concentrations (EDWCs) used in the dietary exposure risk assessment were provided by EFED in a memorandum dated 4/15/09 (Memo, G. Orrick; DP# 349860). Water residues were incorporated directly into the DEEM-FCID™ in the food categories "water, direct, all sources" and "water, indirect, all sources."

Screening EDWCs (Table 5.1.9) of saflufenacil were generated with FQPA Index Reservoir Screening Tool (FIRST) for surface water and with PRZM GW for ground water. Modeled application rates represent the maximum use patterns of five proposed end-use labels with selected uses on row crops, orchard trees, vineyards, tree plantations, and non-agricultural areas. Remaining model input parameters were chosen according to current guidance (USEPA, 2002). EDWCs reflect exposure to saflufenacil and all degradates of concern in drinking water (Table 5.1.8).

Table 5.1.9. Tiered EDWCs for Proposed Saflufenacil Uses.		
Source (Tier: Model)	**1-in-10-year Peak Exposure (ppb)**	**1-in-10-year Annual Mean Exposure (ppb)**
Surface water (Tier I: FIRST)	37.3	23.8
Ground water (Tier II: PRZM GW)	180	173

5.1.10 Food Residue Profile

The submitted magnitude of the residue data for the raw and processed commodities of legume vegetables, citrus fruit, pome fruit, stone fruit, tree nuts, cereal grains, cotton, sunflowers, and grapes are adequate. There are also adequate storage stability data to validate the storage conditions and intervals of samples collected from the field and processing trials. As no concentration of the total saflufenacil residue was found in any processed commodity, separate tolerances for residues in/on processed commodities are not required.

An adequate dairy cow feeding study has been submitted; this study is acceptable for determining tolerance levels for ruminant commodities. Based on the submitted data, HED has concluded that the tolerances, expressed as saflufenacil *per se*, are required for ruminant commodities. Based on the results of the laying hen metabolism study and the proposed tolerances in poultry feed components, there is no reasonable expectation of finite residues of saflufenacil in the meat, meat byproducts, and eggs of poultry as a result of the proposed uses.

A summary of the recommended tolerances for the current petition are listed in Appendix C: Tolerance Reassessment Summary. The petitioner should submit a revised Section F reflecting the recommended tolerances and commodity definitions presented in Appendix C.

5.1.11 International Residue Limits

There are no Codex, Canadian, or Mexican maximum residue limits (MRLs) established for residues of saflufenacil and its metabolites in crops or livestock commodities. The residue definition and recommended tolerances are harmonized with Canada and Australia.

5.2 Dietary Exposure and Risk

5.2.1 Acute Dietary Exposure/Risk

The unrefined acute analysis assumed 100% CT, DEEM™ 7.81 default concentration factors, and tolerance-level residues for all commodities. Drinking water was incorporated directly into the dietary assessment using the concentration for ground water generated by the Tier II PRZM GW (180 ppb). The acute dietary exposure and risk estimates (food + drinking water) are 0.010051 mg/kg/day for the general U.S. population (<1% of the aPAD) and 0.036991 mg/kg/day (<1% of the aPAD) for the most highly exposed population subgroup (all infants (<1 year old)) and are thus below HED's LOC (<100% aPAD; Table 5.2).

5.2.2 Chronic Dietary Exposure/Risk

The unrefined chronic analysis assumed 100% CT, DEEM™ 7.81 default concentration factors, and tolerance-level residues for all commodities. Drinking water was incorporated directly into the dietary assessment using the concentration for ground water generated by PRZM GW (173 ppb). The chronic dietary exposure and risk estimates (food + drinking water) are 0.004043

mg/kg/day for the general U.S. population (8.8% of the cPAD) and 0.012951 mg/kg/day (28% of the cPAD) for the most highly exposed population subgroup (all infants (<1 year old)) and are thus below HED's LOC (<100% cPAD; Table 5.2).

Table 5.2. Summary of Dietary (Food and Drinking Water) Exposure Risk for Saflufenacil.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.010051	<1	0.004043	8.8
All Infants (<1 year old)	**0.036991**	<1	**0.012951**	**28**
Children 1-2 years old	0.016375	<1	0.006895	15
Children 3-5 years old	0.014835	<1	0.006176	13
Children 6-12 years old	0.010181	<1	0.004141	9.0
Youth 13-19 years old	0.008192	<1	0.003002	6.5
Adults 20-49 years old	0.009009	<1	0.003672	8.0
Adults 50+ years old	0.008151	<1	0.003821	8.3
Females 13-49 years old	0.009122	<1	0.003659	8.0

*The values for the highest exposed population for each type of risk assessment are bolded.

5.2.3 Cancer Dietary Risk

Saflufenacil is classified as "not likely carcinogenic to humans." Therefore, cancer risk is not a concern for this chemical.

5.3 Anticipated Residue and %CT Information

The acute and chronic dietary exposure analyses were based on tolerance-level residues and the assumption of 100% CT. Anticipated residues and percent CT estimates were not incorporated into the assessments.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

As saflufenacil is a new active ingredient with no registered or proposed residential uses, a quantitative non-occupational exposure assessment was not performed.

6.1 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for saflufenacil. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management

practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT® computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

Aggregate exposure and risk assessments were assessed by incorporating the drinking water directly into the dietary-exposure assessment for the following scenarios: acute and chronic aggregate exposure (food + drinking water). Short-, intermediate-, and long-term aggregate-risk assessments were not performed because there are no registered or proposed uses of saflufenacil which result in residential exposures. A cancer aggregate-risk assessment was not performed because saflufenacil is not a carcinogen and cancer risk is not a concern.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to saflufenacil and any other substances and saflufenacil does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that saflufenacil has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

The following reference applies to this section:
Occupational and Residential Exposure Assessment - D349939, K. Lowe., pending

9.1 Short-/Intermediate-Term Occupational Handler Risk

Exposure of saflufenacil handlers may occur from applications to agricultural crops and non-crop use sites. Handler's exposure and risk were estimated for the following scenarios:

Mixer/Loader:
(1a) Open mixing/loading liquids for aerial application;
(1b) Open mixing/loading liquids for chemigation;
(1c) Open mixing/loading liquids for groundboom application;
(1d) Open mixing/loading liquids for rights-of-way application;
(1e) Open mixing/loading dry flowables for aerial application;

(1f) Open mixing/loading dry flowables for groundboom application;
(1g) Impregnating liquids onto dry bulk fertilizer in commercial settings;
(1h) Impregnating liquids onto dry bulk fertilizer on farm;

Applicator:
(2) Applying sprays via aerial applications;
(3) Applying sprays via groundboom applications;
(4) Applying sprays via rights-of-way sprayer;
(5) Applying impregnated dry bulk fertilizer with commercial equipment;
(6) Applying impregnated dry bulk fertilizer with grower-owned equipment; and

Mixer/Loader/Applicator:
(7) Open mixing/loading/applying via low-pressure handwand.

The minimum level of PPE for handlers is based on acute toxicity for the end-use product. For pesticide handlers, HED presents estimates of dermal exposure for "baseline" (i.e., workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves), as well as for "baseline" and the use of protective gloves or other PPE, as might be necessary. The saflufenacil product labels direct applicators and other handlers to wear:

- BAS 800 01H TNV; BAS 800 04H FiRoCrop; BAS 804 00H LegVeg; BAS 781 02H: long-sleeve shirt, long pants, chemical-resistant gloves, shoes plus socks and protective eyewear.
- BAS 800 02H: coveralls, short-sleeve shirt, short pants, chemical-resistant gloves, shoes plus socks, protective eyewear.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. In accordance with HED's Science Advisory Council for Exposure (ExpoSAC) policy, exposure data from PHED Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98), were used with other HED standard values for acres treated per day, body weight, and the level of PPE to assess handler exposures.

There are no data to assess impregnating liquids onto dry bulk fertilizer in commercial settings. The assumptions that the amount of saflufenacil handled per day in commercial settings (500–960 tons) make it unlikely that open mixing/loading is used for this use. Therefore, as a reasonable surrogate for impregnation of dry bulk fertilizer in commercial settings, unit exposure values from PHED for engineering controls (closed mixing/loading) are used.

Handler exposure is expected to be short- or intermediate-term based on information provided on proposed labels. In addition, the short- and intermediate-term toxicological endpoints are the same; therefore, the estimates of risk for short-term duration exposures are protective of those for intermediate-term duration exposures. Long-term exposures are not expected, therefore, a long-term assessment was not conducted. The average adult body weight of 60 kg was used for estimating dermal and inhalation dose because the endpoint is from a development study and was observed in the fetuses.

Daily dermal or inhalation handler exposures are estimated for each applicable handler task with the application rate, the area treated in a day, and the applicable dermal or inhalation unit exposure using the following formula:

Daily Exposure (mg ai/day) = Unit Exposure (mg ai/lb ai handled) x Application Rate (lbs ai/area) x Daily Area Treated (area/day)

Where:

Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Unit Exposure	=	Unit exposure value (mg ai/lb ai) derived from August 1998 PHED data;
Application Rate	=	Normalized application rate based on a logical unit treatment, such as acres; and
Daily Area Treated	=	Normalized application area based on a logical unit treatment such as acres (A/day).

The daily dermal or inhalation dose is calculated by normalizing the daily exposure by body weight and adjusting, if necessary, with an appropriate dermal or inhalation absorption factor using the following formula:

Average Daily Dose (mg/kg/day) = Daily Exposure (mg ai/day) x (Absorption Factor (%/100)) / Body Weight (kg)

Where:

Average Daily Dose	=	Absorbed dose received from exposure to a pesticide in a given scenario (mg ai/kg body weight/day);
Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Absorption Factor	=	A measure of the amount of chemical that crosses a biological boundary such as the skin or lungs (% of the total available absorbed); and
Body Weight	=	Body weight determined to represent the population of interest in a risk assessment (kg).

Non-cancer dermal and inhalation risks for each applicable handler scenario are calculated using a MOE, which is a ratio of the NOAEL to the daily dose. All MOE values were calculated using the formula below:

MOE = NOAEL or LOAEL (mg/kg/day) / Average Daily Dose (mg/kg/day)

Dermal and inhalation risks were combined in this assessment, since the toxicological effects for these exposure routes were similar (decreased body weight and body-weight gains). Dermal and inhalation risks were combined using the following formula:

Total MOE = NOAEL (mg/kg/day) / Combined Dose (dermal + inhalation, mg/kg/day)

Table 9.1 presents the estimated risks for workers based on the short- and intermediate-term dermal and inhalation exposures at baseline. HED has determined that risks are not of concern (i.e., MOEs >100), **provided workers wear protective gloves as recommended on the label. The RD should ensure that the PPE listed on the BAS 800 02H label (i.e., coveralls over short-sleeve shirt and short pants) is the correct PPE for that product.**

It should be noted that only engineering control data are available to assess dermal and inhalation risks to handlers operating aircraft (enclosed cockpit) and to commercial handlers participating in

dry bulk fertilizer impregnation (closed mixing/loading/application systems). The risks are not of concern for pilots using enclosed cockpits and for commercial handlers involved in dry bulk fertilizer impregnation using closed mixing/loading/application systems and wearing baseline attire.

Table 9.1. Occupational Handler Dermal and Inhalation Exposures and Risks.

Exposure Scenario	Application rate[a] (lb ai/acre)	Dermal and Inhalation Unit Exposures (mg/lb ai)	Area Treated Daily (acres)[b]	Combined Doses (mg/kg/day)[c]	Total MOE[d]
Mixer/Loaders					
Mixing/Loading Liquids for Aerial Applications (PHED)	0.35	Dermal Baseline[e]: 2.9 (HC)[i] Single layer w/gloves[g]: 0.023 (HC) Inhalation Baseline[f]: 0.0012 (HC)	1,200	Baseline Dermal + Baseline Inhalation: 0.6200 Single layer w/gloves dermal + Baseline Inhalation: 0.013	Baseline Dermal + Baseline Inhalation: **8.1** Single layer w/gloves dermal + Baseline Inhalation: 380
Mixing/Loading Liquids for Chemigation Applications (PHED)	0.111		350	Baseline Dermal + Baseline Inhalation: 0.0570 Single layer w/gloves dermal + Baseline Inhalation: 0.0012	Baseline Dermal + Baseline Inhalation: **88** Single layer w/gloves dermal + Baseline Inhalation: 4,200
Mixing/Loading Liquids for Groundboom Applications (PHED)	0.35		200	Baseline Dermal + Baseline Inhalation: 0.100 Single layer w/gloves dermal + Baseline Inhalation: 0.0022	Baseline Dermal + Baseline Inhalation: **49** Single layer w/gloves dermal + Baseline Inhalation: 2,300
Mixing/Loading Liquids to Support Rights of Way	0.35		80	Baseline Dermal + Baseline Inhalation: 0.041	Baseline Dermal + Baseline Inhalation: 120
Mixing/Loading Liquids for Commercial Impregnation of Dry Bulk Fertilizers (PHED eng control for M/L liquids)	1.34 lb ai/ton	Dermal Engineering control: 0.0086 Inhalation Engineering control: 0.000083	960 tons	Engineering control dermal + inhalation: 0.0073	Engineering control dermal + inhalation: 680
Mixing/Loading Liquids for Commercial Impregnation of Dry Bulk Fertilizers (PHED eng control for M/L liquids)	1.34 lb ai/ton	Dermal Engineering control: 0.0086 Inhalation Engineering control: 0.000083	500 tons	Engineering control dermal + inhalation: 0.0038	Engineering control dermal + inhalation: 1,300
Mixing/Loading Liquids for On-farm Impregnation of Dry Bulk Fertilizers (PHED M/L liquids)	0.134	Dermal Baseline: 2.9 (HC)[i] Inhalation Baseline: 0.0012 (HC)	160	Baseline Dermal + Baseline Inhalation: 0.032	Baseline Dermal + Baseline Inhalation: 160

Table 9.1. Occupational Handler Dermal and Inhalation Exposures and Risks.

Exposure Scenario	Application rate[a] (lb ai/acre)	Dermal and Inhalation Unit Exposures (mg/lb ai)	Area Treated Daily (acres)[b]	Combined Doses (mg/kg/day)[c]	Total MOE[d]
Mixing/Loading Liquids for On-farm Impregnation of Dry Bulk Fertilizers (PHED M/L liquids)	0.134	Dermal Baseline: 2.9 (HC)[i] Inhalation Baseline: 0.0012 (HC)	80	Baseline Dermal + Baseline Inhalation: 0.016	Baseline Dermal + Baseline Inhalation: 320
Mixing/Loading Dry Flowables for Aerial Applications (PHED)	0.022	Dermal Baseline: 2.9 (HC)[i] Inhalation Baseline: 0.0012 (HC)	1,200	Baseline Dermal + Baseline Inhalation: 0.0012	Baseline Dermal + Baseline Inhalation: 4,100
Mixing/Loading Dry Flowables for Groundboom Applications (PHED)	0.044	Dermal Baseline: 2.9 (HC)[i] Inhalation Baseline: 0.0012 (HC)	80	Baseline Dermal + Baseline Inhalation: 0.0002	Baseline Dermal + Baseline Inhalation: 31,000
Applicators					
Applying Sprays via Aerial Equipment (PHED)	0.35	Dermal Eng control[h]: 0.005 (MC) Inhalation Eng control[h]: 0.000068 (MC)	1,200	Eng control Dermal + Inhalation: 0.0015	Eng control Dermal + Inhalation: 3,300
Applying Sprays via Groundboom Equipment (PHED)	0.35	Dermal Baseline: 0.014 (HC) Inhalation Baseline: 0.00074 (HC)	200	Baseline Dermal + Baseline Inhalation: 0.0014	Baseline Dermal + Baseline Inhalation: 3,700
Applying Sprays via Rights of Way Equipment (PHED)	0.35	Dermal Baseline: 1.3 (LC) Inhalation Baseline: 0.0039 (HC)	80	Baseline Dermal + Baseline Inhalation: 0.02	Baseline Dermal + Baseline Inhalation: 250
Commercial Application of Dry Bulk Fertilizers (PHED tractor-drawn granular spreader data)	0.134	Dermal Baseline: 0.0099 (LC) Inhalation Baseline: 0.0012 (LC)	320	Baseline Dermal + Baseline Inhalation: 0.0011	Baseline Dermal + Baseline Inhalation: 4,700
			160	Baseline Dermal + Baseline Inhalation: 0.0005	Baseline Dermal + Baseline Inhalation: 9,300
On-farm Applications of Dry Bulk Fertilizers (PHED tractor-drawn granular spreader data)	0.134	Dermal Baseline: 0.0099 (LC) Inhalation Baseline: 0.0012 (LC)	160	Baseline Dermal + Baseline Inhalation: 0.0005	Baseline Dermal + Baseline Inhalation: 9,300
			80	Baseline Dermal + Baseline Inhalation: 0.0003	Baseline Dermal + Baseline Inhalation: 19,000
Flaggers					
Flagging for Aerial Sprays Applications (PHED)	0.35	Dermal Baseline: 0.011 (HC) Inhalation Baseline: 0.00035 (HC)	350	Baseline Dermal + Baseline Inhalation: 0.0014	Baseline Dermal + Baseline Inhalation: 3,600

Table 9.1. Occupational Handler Dermal and Inhalation Exposures and Risks.

Exposure Scenario	Application rate[a] (lb ai/acre)	Dermal and Inhalation Unit Exposures (mg/lb ai)	Area Treated Daily (acres)[b]	Combined Doses (mg/kg/day)[c]	Total MOE[d]
Mixer/Loader/Applicators					
Mixing/Loading/ Applying Liquids with Low Pressure Handwand (PHED)	0.35	Dermal Baseline: 100 (LC) Inhalation Baseline: 0.03 (MC)	2	Baseline Dermal + Baseline Inhalation: 0.0350	Baseline Dermal + Baseline Inhalation: 140

a. Application rates based on proposed uses on labels for saflufenacil. Units = lb ai/acre unless noted otherwise.
b. ExpoSAC Policy # 9.1.
c. Combined Dose (mg/kg/day) = Dermal + Inhalation doses. Dose = daily unit exposure (mg/lb ai) x application rate (lb ai/acre) x acres treated x absorption factor (dermal: 3%; inhalation: 100%) / body weight (60-kg adult female).
d. Total MOE = NOAEL (5 mg/kg/day) / Combined Dose (mg/kg/day).
e. Baseline Dermal: long-sleeve shirt, long pants, and no gloves.
f. Baseline Inhalation: no respirator.
g. Single layer w/ gloves: Baseline plus chemical-resistant gloves.
h. Engineering control for applying sprays via aerial equipment: enclosed cockpit.
i. Data confidence: HC = high confidence; MC = medium confidence; LC = low confidence

9.2 Short-/Intermediate-Term Postapplication Risk

HED assumes that inhalation exposures are minimal following outdoor applications of an active ingredient with low vapor pressure. Since saflufenacil is applied only in outdoor settings and has a low vapor pressure (2.0×10^{-15} Pa @ 25°C), postapplication inhalation exposures and risks were not assessed.

Most of the proposed uses for saflufenacil are soil-directed preplant or preemergent uses where no crop foliage is present. The proposed labels indicate that crop injury will result if the products are applied postemergent (over the top) to any crop. Currently, HED has no transfer coefficients or other data to assess postapplication dermal exposures from soil by occupational workers. In general, such exposures are considered to be negligible. Therefore, for the proposed soil-directed uses, postapplication dermal exposures and risks to occupational workers were not assessed. For the use on sunflowers as a desiccant, postapplication exposure is expected to be minimal since harvesting of sunflowers is typically done by machine.

The proposed labels have 12- and 24-hour REIs. The technical material has a Toxicity Category III for acute oral, acute dermal and acute eye irritation. It has a Toxicity Category IV for acute inhalation and acute dermal irritation. Per the WPS, a 12-hour REI is required for chemicals classified under Toxicity Category III and IV. Therefore, the REI of 12 hours appearing on the proposed saflufenacil labels are in compliance with the WPS. **The RD should ensure that the 24-hour REI appearing on the BAS 800 02H and BAS 781 02H labels is correct.**

10.0 Data Needs and Label Recommendations

10.1 Toxicology

- As part of the new 40 CFR revised Part 158 requirement, an immunotoxicity study is required.

10.2 Residue Chemistry

860.1200 Directions for Use

- The BAS 800 04H FiRoCrop Herbicide contains directions for use on varieties of forage sorghum. However, forage sorghum is a member of the grass crop group, for which no data were submitted or tolerances proposed. The BAS 800 04H FiRoCrop Herbicide label should thus be amended to limit the sorghum use to sweet and grain varieties only.

- All of the sunflower field trials were performed with a WG formulation; whereas, the proposed use is for the SC formulation. These formulation types are not considered to be equivalent for mid- to late-season foliar applications. The proposed sunflower use should thus be removed from the BAS 800 04H FiRoCrop Herbicide (SC) label and may be added to the BAS 800 01H TNV Herbicide (WG) label. Alternatively, bridging trials could be performed to determine the effect of the formulation type on residue levels.

860.1650 Submittal of Analytical Reference Standards

- Analytical standards for of saflufenacil, M800H11, and M800H35 are currently available in the National Pesticide Standards Repository [Source: personal communication with T. Cole of ACL/BEAD, 1/15/09]. However, since the standards for M800H11 and M800H35 expired on 10/1/08, the petitioner is requested to provide a new supply to the Repository.

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F specifying the following:

- The tolerance expression for plant commodities should be revised to: "Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of saflufenacil (2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide) and its metabolites *N*-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2*H*)-pyrimidinyl)-4-fluorobenzoyl]-*N*'-isopropylsulfamide and *N*-[4-chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino}carbonyl)phenyl]urea, calculated as the stoichiometric equivalent of saflufenacil, in or on the commodities."

- The tolerance expression for livestock commodities should be revised to: "Tolerances are established for residues of saflufenacil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only saflufenacil, 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino]sulfonyl]benzamide, in or on the commodities."

- Revised tolerance levels and commodity definitions are presented in Appendix C: Tolerance Summary Table.

10.3 Occupational and Residential Exposure

- The RD should ensure that the PPE listed on the BAS 800 02H label is the correct PPE for this product.

- The RD should ensure that the REIs listed on the BAS 800 02H and BAS 781 02H labels are correct for those two products.

References:

Saflufenacil in/on Legume Vegetables (group 06), the Foliage of Legume Vegetables (group 07), Citrus Fruits (group 10), Pome Fruits (group 11), Stone Fruits (group 12), Tree Nuts (group14), Cereal Grains (group 15), Forage, Fodder and Straw of Cereal Grains (group 16), Sorghum Stover, Undelinted Cotton Seed, Cotton Gin Byproducts, Grapes, Almond Hulls, Sunflower Seed, and Livestock Commodities. **Summary of Analytical Chemistry and Residue Data**. G. Kramer. D349938.

Saflufenacil. Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action in/on Legume Vegetables (group 06), the Foliage of Legume Vegetables (group 07), Citrus Fruits (group 10), Pome Fruits (group 11), Stone Fruits (group 12), Tree Nuts (group14), Cereal Grains (group 15), Forage, Fodder and Straw of Cereal Grains (group 16), Sorghum Stover, Undelinted Cotton Seed, Cotton Gin Byproducts, Grapes, Almond Hulls, Sunflower Seed, and Livestock Commodities. G. Kramer. D364183.

BAS 800 H (Saflufenacil): Occupational Exposure/Risk Assessment of Proposed Section 3 Uses on Various Agricultural Crops and Non-Agricultural Sites. K. Lowe. D349939

Tiered Drinking Water Exposure Assessment for Saflufenacil (Section 3 New Chemical Uses on Agricultural and Non-agricultural Areas). G. Orrick. D349860

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for use on food for saflufenacil are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	no	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
870.7800	Immunotoxicity	yes	no
Special Studies for Ocular Effects Acute Oral (rat) Subchronic Oral (rat) Six-month Oral (dog)		-	-

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Saflufenacil.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category	Purity
870.1100	Acute oral [rat]	47128101	LD50 was >2000 mg/kg bw	III	93.8%
870.1200	Acute dermal [rat]	47128102	LD_{50} >2000 mg/kg	III	93.8%
870.1300	Acute inhalation [rat]	47128103	LC_{50} >5.3 mg/L	IV	93.8%
870.2400	Acute eye irritation [White New Zealand rabbit]	47128105	minimal irritation	III	93.8%
870.2400	Acute eye irritation [White New Zealand rabbit]	47128104	minimal irritation	III	93.8%
870.2500	Acute dermal irritation [rabbit]	47128106	slightly irritating	IV	93.8%
870.2600	Skin sensitization [Guinea Pig]	47128107	not a sensitizer	N/A	93.8%

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Saflufenacil.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 28-Day Oral Toxicity feeding-mice	47128110 (2007) Acceptable/non-guideline 0, 50, 150, 450, 1350, or 4050 ppm M\F: 0, 12.8/17.9, 36.6/63.4, 112/153.1, 335/446, 882/1630 mg/kg bw/day.	LOAEL = 36.6 mg/kg bw/day (males) based on increased alanine aminotransferase, aspartate aminotransferase, urea and total bilirubin, decreased hemoglobin and Ht and increased liver weight and centrilobular fatty change. NOAEL = 12.8 mg/kg bw/day. LOAEL = 153.1 mg/kg bw/day (females) based on moderate centrilobular fatty change in the liver. NOAEL = 63.4 mg/kg bw/day.
870.3100 28-Day Oral Toxicity feeding-rat	47128108 (2007) Acceptable/non-guideline 0, 50, 150, 450, 1350, or 4050 ppm M = 0, 4.5, 13.4, 39.2, 117, 357; F = 0, 5.0, 15.9, 43.6, 130.4, 376 mg/kg bw/day.	LOAEL = 39.2 mg/kg bw/day (males) based on decreased Hb, MCV, and MCH. NOAEL =13.4 mg/kg bw/day. LOAEL = 130.4 mg/kg bw/day (females) based on decreased Hb, Ht, MCV, and MCH. NOAEL = 43.6 mg/kg bw/day.
870.3100 90-Day Oral Toxicity feeding-mice	47128111 (2007) Acceptable/guideline 0, 15 (males only), 50, 150, 450, and 1350 (females only) ppm M = 0, 3.6, 12.4, 36.7, 109.1; F = 0, 17.6, 51.8, 156.6, 471.2 mg/kg bw/day	LOAEL = 36.7mg/kg bw/day (males) based on multiple hematological changes, liver weight increases with centrilobular fatty change and lymphoid infiltrate in males. NOAEL = 12.4mg/kg bw/day. LOAEL = 156.6 mg/kg/day (females) based on increased liver weight with centrilobular fatty

		change and lymphoid infiltrate. NOAEL = 51.8 mg/kg/day.
870.3100 90-Day Oral Toxicity feeding-rat	47128109 (2007) Acceptable/guideline 0, 50, 150, 450 (males), 1350, or 4050 (females) ppm M =0, 3.5, 10.5, 32.3, 94.7 F = 0, 4.3, 12.6, 110.5, 344.7 mg/kg bw/day.	LOAEL = 32.3 mg/kg bw/day (M) and 110.5 mg/kg bw/day (F) based on multiple hematological effects and increased spleen weight and extramedullary hematopoiesis. NOAEL = 10.5 (M), 12.6 mg/kg bw/day (F).
870.3150 28-Day Oral Toxicity feeding-dog	47128112 (2005) Acceptable/non-guideline 0, 30, 100, or 300 mg/kg bw/day.	LOAEL = 100 mg/kg bw/day based decreased mean corpuscular volume, MCH, and MCHC, bone marrow hyperplasia, increased iron storage in the liver and extramedullary hematopoiesis in the spleen. NOAEL = 30 mg/kg bw/day.
870.3150 90-Day Oral Toxicity feeding-dog	47128113 (2006) Acceptable/guideline 0, 10, 50, or 150 mg/kg bw/day	LOAEL = 50 mg/kg bw/day based on lower MCV and MCH values in both sexes. NOAEL = 10 mg/kg bw/day.
870.3200 21/28-Day dermal toxicity (rat)	47128114 (2006) Acceptable/guideline 0, 100, 300, or 1000 mg/kg	LOAEL was not established. NOAEL = 1000 mg/kg bw/day.
870.3700a Prenatal developmental in (rat)	47128115 (2007) Acceptable/guideline 0, 5, 20, or 60mg/kg/day	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 60 mg/kg/day based on decrease hemoglobin and Ht, mean corpuscular volume and MCH. **Developmental** NOAEL = 5 mg/kg/day LOAEL = 20 mg/kg/day based on based on decreased fetal body weights and increase skeletal variations.
870.3700b Prenatal developmental in (rabbit)	47128116 (2006) Acceptable/guideline 0, 50, 200, or 600 mg/kg/day	**Maternal** NOAEL = 200 mg/kg bw/day LOAEL = 600 mg/kg bw/d based on mortality and increased necropsy findings. **Developmental** NOAEL = 50 mg/kg/day LOAEL = 200 mg/kg/day based on increased liver porphyrins.
870.3800 Reproduction and fertility effects (rat)	47128117 (2007) acceptable/guideline 0, 5, 15, or 50 mg/kg bw/day	**Parental Systemic** NOAEL = 15 mg/kg/day **Parental Systemic** LOAEL = 50 mg/kg/day based on decreased food intake, body weight, body weight gain and changes in hematological parameters and organ weights indicative of anemia. **Reproduction** NOAEL = M/F 50

		mg/kg/day **Reproduction** LOAEL was not established. **Offspring** NOAEL = 15 mg/kg/day **Offspring** LOAEL = 50 mg/kg/day based on decreased number of live born pups, increased number of stillborn pups, decreased viability and lactation indices, decreased pre-weaning body weight and/or body weight gain and changes in hematological parameters.
870.4300b Chronic Toxicity (dog)	47128118 (2007) Acceptable/guideline 0, 5, 20, or 80 mg/kg bw/day	LOAEL = 80 mg/kg bw/day based on decreased albumin, MVH, and MCH. NOAEL = 20 mg/kg bw/day.
870.4300 Chronic/Carcinogenicity (rat)	47128120 (2007) Acceptable/guideline 0, 20, 100, 250 (males), 500 or 1000 (females) ppm M = 0, 0.9, 4.8, 12.0, 24.2 F = 0, 1.3, 6.2, 31.4, 63.0 mg/kg bw/day.	LOAEL = 31.4 mg/kg bw/day (females) based on decreased hemoglobin, Ht, MCV and MCH. NOAEL = 6.2 mg/kg bw/day (females). LOAEL was not established in males. NOAEL = 24.2 mg/kg bw/day. **No evidence of carcinogenicity**
870.4300 Chronic/Carcinogenicity (mouse)	47128119 (2007) Acceptable/guideline 0, 1 (males), 5, 25, 75, or 150 (females) ppm M = 0, 0.2, 0.9, 4.6, 13.8 F = 0, 1.2, 6.4, 18.9, 38.1 mg/kg bw/day. satellite groups: M = 0, 14.2 F = 0, 39.0 mg/kg bw/d	NOAEL = 4.6 mg/kg bw/day (males) and 18.9 mg/kg bw/day (females). LOAELs = 13.8 mg/kg bw/day (males) and 38.1 mg/kg bw/day (females) based on decreased red blood cells, hemoglobin, and Ht and porphyria observed in the satellite group. **No evidence of carcinogenicity**
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47128121 (2005) Acceptable/guideline 0, 20, 100, 500, 2500, or 5000 µg/plate (saflufenacil hydrate)	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47128122 (2005) Acceptable/guideline 0, 20, 100, 500, 2500, or 5000 µg/plate (saflufenacil anhydrate)	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47128123 (2005) Acceptable/guideline 0, 312.5, 625, 1250, 2500, or 5000 µg/mL	There was no evidence of induced mutant colonies over background.
Cytogenetics 870.5375 *In vitro* Mammalian Cytogenetics chromosomal aberration assay-V79 cells	47128124 (2005) Acceptable/guideline 0, 5, 10, and 20 ug/ml without S9 activation 0, 10, 20, and 40 ug/ml with S9	Saflufenacil was considered clastogenic in vitro in V79 cells in the presence of S9 metabolic activation. Saflufenacil was not clastogenic in the absence of

	activation	metabolic activation.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in mice	47128125 (2005) Acceptable/guideline 0, 500, 1000, or 2000 mg/kg bw.	There was no increase in the frequency of micronucleated immature erythrocytes in mouse bone marrow.
870.5550 Other Genotoxicity-*In vivo* unscheduled DNA synthesis (rat)	47128126 (2005) Acceptable/guideline single oral dose of 1000, or 2000 mg/kg bw	Negative
870.6200a Acute neurotoxicity battery (rat)	47128127 (2007) Acceptable/Guideline 0, 125, 500, or 2000 mg/kg bw	Systemic LOAEL was 2000 mg/kg bw (males) based on the decreased motor activity representing mild and transient systemic toxicity. Systemic LOAEL was not established for females. Systemic NOAEL = 500 (M) and 2000 (F) mg/kg bw. There was no evidence of neurotoxicity.
870.6200b Subchronic neurotoxicity (rat)	47128128 (2007) Acceptable/Guideline 0, 50, 250, 1000 (males), or 1350 (females) ppm M = 0, 3.3, 16.6, 66.2 F = 0, 3.9, 19.4, 101.0 mg/kg bw/d.	Systemic NOAEL = 16.6 (males), 19.4 (females) mg/kg bw/day. Systemic LOAEL = 66.2 (males) and 101 (females) mg/kg bw/day based on decreased hemoglobin, Ht, mean corpuscular volume and MCH. There was no evidence of neurotoxicity.
870.7485 Metabolism and pharmacokinetics (rat)	47128130, 47128129 (2007) 4, 20, or 100 mg/kg bw (single oral dose) 5 or 100 mg/kg bw (single dose) 100 mg/kg for 14 days	Saflufenacil was rapidly absorbed, distributed, and excreted. Regardless of the dose administered, maximum concentration of saflufenacil in blood and plasma was reached within 1 h of dosing and declined rapidly after 24 h. Excretion of orally dosed saflufenacil was essentially complete within 96 h; the majority was eliminated within the first 24 to 48 h. Demonstrating that the majority of the saflufenacil residues occurred in the plasma and was not bound to cellular elements of the blood. There was a sex-dependent difference in the excretion of orally administered saflufenacil. Following single low- and high-dose administration or a repeat high-dose administration, the main route of elimination in male rats was via the feces, while urinary excretion was the major route of elimination in females. There was significantly higher biliary

		excretion of saflufenacil residues in males than in females. Exhalation was not a relevant excretion pathway of saflufenacil. At 168 h after dosing, saflufenacil residues remaining in tissues were very low, and occurred mainly in carcass, liver, skin, and gut contents. Saflufenacil was metabolized by three major transformation steps: demethylation of the uracil ring system, degradation of the *N*-methyl-*N*-isopropyl group to NH_2, and cleavage of the uracil ring, forming a sulfonylamide group. The predominant metabolites were M800H01, M800H03, M800H07 and the parent compound. Other minor metabolites were M800H05, M800H16, M800H17, M800H18, M800M19, and M800M20. There were no significant sex differences in metabolic profiles.
870.7600 Dermal penetration (rat)	47128214 (2007) Acceptable/guideline 1.1723 mg/cm^2, 0,1172 mg/cm^2 and 0.0117 mg/cm^2 11.723, 1.172 and 0.117 mg/rat	Dermal absorption is 3%.
Comparative Bioavailability/Toxicity Study (rat)	47128133 (2005) Acceptable/non-guideline 0 or 1350 ppm	The bioavailability and toxicity potential of the hydrated and anhydrated forms of saflufenacil were similar.
Mechanistic study – total porphyrin analysis in rat	47128132 (2006) Acceptable/non-guideline 0, 10, 50, or 1000 ppm (♂ = 0, 0.8, 4.1, 80.6; ♀ = 0, 0.9, 4.6, 89.5 mg/kg bw/day, respectively)	Total porphyrins in feces and liver provided the most reliable and sensitive data. Statistically significant effects on porphyrin metabolism could be detected at exposure concentrations well below those associated with adverse hematological effects. NOAEL= 4.1 mg/kg/day LOAEL = 80.6 mg/kg/day based on decreased hemoglobin, Ht, MCV, MCH, and MCHC.
Mechanistic study-porphyrin analysis supplementary (rat)	47128131 (2005) Acceptable/non-guideline 0, 1, 5, or 25 ppm (♂ = 0, 0.1, 0.4, 2.0; ♀ = 0, 0.1, 0.5, 2.3 mg/kg bw/day	Dietary administration of saflufenacil at 25 ppm caused an increase in porphyrin in feces of male (237%) and female (61%) rats, while saflufenacil at 5 ppm caused an increase in fecal porphyrin only in males. There were no effects on hematology parameters.

A.3 Executive Summaries

870.3100 90-Day Oral Toxicity - Rat

EXECUTIVE SUMMARY: In a 90-day toxicity study (MRID 47128109), BAS 800 H (93.9%, batch lot#) was administered in the diet daily to Wistar rats, 10/sex/group, at nominal concentrations of 0, 50, 150, 450 (♂), 1350, or 4050 (♀) ppm (♂ = 0, 3.5, 10.5, 32.3, 94.7; ♀ = 0, 4.3, 12.6, 110.5, 344.7, respectively).

At 4050 ppm (♀ only), two females died. Clinical signs of toxicity observed included reduced general condition, severe skin paleness, anogenital urine smear, and piloerection. Food consumption was significantly reduced and there was significant reduction in body weight and body-weight gain. Due to the severe toxicological effects, this dose level was terminated on day 53. There were no treatment-related findings at 50 or 150 ppm. No clinical signs of toxicity were observed at ≤450 ppm. At 450 ppm (♂ only), treatment-related findings were increased spleen weight (13%) correlated with extramedullary hematopoiesis (4 vs 1/10 in controls). At 1350 ppm, males showed isolated incidences of skin paleness and piloerection, reduced motor activity, decreased body weight and body weight gain (7-14%), lowered food consumption (8-11%), increased absolute and relative spleen weight (116-137%) correlated with marked extramedullary hematopoiesis (4 vs 1/10 in controls). Females exhibited anogenital urine smears and increased spleen weight (16%) correlated with marked extramedullary hematopoiesis (3-5 vs 1/10 in controls) and increased iron storage. Affected hematological and clinical chemistry parameters were decreased hemoglobin (16-26%, ♂♀), Ht (14-17%, ♂♀), mean corpuscular volume (MCV) (13-15%, ♂♀), MCH (16-25%, ♂♀), MCHC (3-12%, ♂♀), total protein and globulins (5-6%, ♂), increased normoblasts and reticulocytes (♂,205%%; ♀, 38%), total bilirubin (59%), urinary transitional epithelial cells (9-10 vs 3/10 in controls >2, ♂), and urinary casts (10 vs 2/10 in controls >1, ♂).

The LOAELs established in males and females were 450 (32.3 mg/kg bw/d) and 1350 ppm (110.5 mg/kg bw/d), respectively, based on multiple hematological effects and histopathology of the spleen. A NOAEL of 150 ppm (♂ = 10.5, ♀ = 12.6 mg/kg bw/d) was established.

This 90-day oral toxicity study in the rat is an acceptable guideline study and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the rat.

870.3100 90-Day Oral Toxicity - Mouse

EXECUTIVE SUMMARY: In a 90-day toxicity study (MRID 47128111), BAS 800 H (93.9%, batch lot#) was administered in the diet daily to groups C57BL/6NCrl mice, 10/sex/group, at 0, 15 (males only), 50, 150, 450 and 1350 (females only) ppm (♂ = 0, 3.6, 12.4, 36.7, 109.1; ♀ = 0, 17.6, 51.8, 156.6, 471.2 mg/kg bw/d, respectively).

There were no treatment related effects on mortality, clinical signs, food and water consumption, food efficiency, clinical chemistry or gross pathology.

Body weight was decreased 4-8% throughout the study in high dose males. Body weight gain was decreased 14-22% in 150 and 450 ppm males; statistical significance was attained on day 14 only. Statistically significant changes (1-21%) were observed in several hematological parameters (hemoglobin (Hb), Ht, mean corpuscular volume (MCV), MCH, and MCHC and

platelet counts) at doses >50 ppm in males and >1350 ppm in females. Alanine aminotransferase was significantly increased by 192-693% at > 150 ppm in males only. Absolute liver and relative liver and kidney significantly increased in males at 150 and 450 ppm (13-49%) and in females at 450 and 1350 ppm (5-42%). An increased occurrence and severity of diffuse (males)/central (females) fatty change of hepatocytes (1-7 grades 3-5 vs 1-9 grades 1-2 in controls) and lymphoid infiltrate (3-10 vs 0/10 in controls)was observed at 150 and 450 ppm in males and females, respectively.

The LOAEL was 150 ppm (♂ = 36.7mg/kg bw/d) based on multiple hematological changes, liver weight increases with centrilobular fatty change and lymphoid infiltrate in males. The NOAEL was 50 ppm (♂ = 12.5mg/kg bw/d). In females, the LOAEL was 450 ppm (156.6 mg/kg/d) based on increased liver weight with centrilobular fatty change and lymphoid infiltrate. The NOAEL was 150 ppm (51.8 mg/kg/d).

This 90-day oral toxicity study in the mouse is an acceptable guideline study and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in mice.

870.3150 90-Day Oral Toxicity - Dog

EXECUTIVE SUMMARY: In a 90-day toxicity study (MRID 47128113), BAS 800 H (94.2%, Lot#, COD - 000606) was administered daily via gelatin capsules to purebred Beagle dogs, 5/sex/group, at nominal doses of 0, 10, 50, or 150 mg/kg bw/d.

There were no treatment-related effects on mortality, ophthalmoscopy, urinalysis, or gross pathology. Signs of systemic toxicity were evident at 50 and 150 mg/kg bw/d.

At 50 mg/kg bw/d, BAS 800 H resulted in decreased mean corpuscular volume (MCV, 4-7%), mean corpuscular hemoglobin (MCH, 6-8%) and histopathological findings in the liver (iron storage, 3/5 vs 0/5 controls).

At 150 mg/kg bw/d, BAS 800 H lowered body weight (6-7%) and body weight gains (73-110%), slightly decreased food consumption and food efficiency, increased the incidence of dark brown/dark red brown feces (5/5 vs 0/5 controls), changes in hematological parameters associated with moderate-to-severe anemia (decreased values in hemoglobin (14-19%) levels, Hct (10-15%), MCV (9-24%), MCH (13-27%), and mean corpuscular hemoglobin concentration (MCHC, 2-5%) as well as histopathological findings in the liver (iron storage, 4-5/5 vs 0/5 controls), spleen (extramedullary hematopoiesis, 2/5 females vs 0/5 controls) and sternum hyperplasia (2/5 both sexes vs 0/5 controls) and bone marrow (hyperplasia, 2/5 females vs 0/5 controls).

The LOAEL was 50 mg/kg bw/d based on lower MCV and MCH values and increased iron storage in the liver in both sexes and the NOAEL was 10 mg/kg bw/d.

This 90-day oral toxicity study in the dog is acceptable guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in dogs.

870.3200 21/28-Day Dermal Toxicity – Rat

EXECUTIVE SUMMARY: In a 4-week dermal toxicity study (MRID 47128114), BAS 800 H (93.8%, batch/lot# COD-000515) was applied to the shaved skin of 10 Wistar rats/sex/dose at 0, 100, 300, or 1000 mg/kg bw/d, 6 h/d for 5 d/week during a 28-day period.

There were no treatment-related effects on mortality, clinical signs of toxicity, food consumption and food efficiency, skin reaction, ophthalmoscopy, functional observational battery, motor activity, clinical chemistry, gross or histopathology. The only treatment-related finding was a slight but statistically significant decrease in the hemoglobin concentration (3%) in males at 1000 mg/kg bw/d. Effects were not observed in females.

A LOAEL was not established; the NOAEL was 1000 mg/kg bw/d.

This 28-day dermal toxicity study in the rat is acceptable guideline and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

A.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 47128115) BAS 800 H (93.8% a.i., batch/lot # COD - 000515) was administered to 25 Crl:WI(Han) female rats/dose in by gavage at dose levels of 0, 5, 20 or 60 mg/kg bw/day from days 6 through 19 of gestation.

There were no treatment-related effects on body weight, body weight gain, food consumption or gross necropsy. Hemoglobin, Ht, mean cell volume, and mean cell hemoglobin were slightly decreased (4-5%). Total bilirubin was increased by 11-22% at > 20 mg/kg bw/day and liver porphyrins were increased by 4-13-fold at 5 mg/kg bw/d.

The maternal LOAEL is 60 mg/kg bw/day, based on decrease hemoglobin, Ht, mean corpuscular volume, and MCH. The maternal NOAEL is 20 mg/kg bw/day

There was a decrease (8-16%) in male and female fetal body weights at doses ≥ 20 mg/kg bw/d. There was an increased incidence of the following skeletal malformations observed at 60 mg/kg/day: thick humeri (litter incidence: 3/22), bent radii (2/22), ulnas (2/22) and femurs (2/22) and mal-positioned and bipartite sternebrae (1-2/22), the control litter incidence was 0/22. Skeletal variations consisting of bent scapulae (1-3/22), incomplete ossification in the nasal area (4-9/22) and thoracic centra (3-9/22), bassioccipital holes (4/22), dumbbell ossification of lumbar centrum (6/22) and the finding of wavy ribs (16-17/22) were increased at doses ≥ 20 mg/kg bw/d. At 60 mg/kg bw/d there was an increase in supraoccipital and bassoccipital holes (4-20/22), incomplete ossification of the hyoid (2/22) and dumbbell ossification of the lumbar centrum (6/22).

The developmental LOAEL is 20 mg/kg bw/day, based on decreased fetal body weights and increase skeletal variations. The developmental NOAEL is 5 mg/kg bw/day.

The developmental toxicity study in the rat is classified acceptable, guideline; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 47128116) BAS 800 H (93.8% a.i., batch/lot # COD - 000515) was administered to 25 female Crl:CHBB(HM) rabbits/dose by gavage at nominal dose levels of 0, 50, 200 or 600 mg/kg bw/day from days 6 through 28 of gestation.

There was an increase in maternal mortality at 600 mg/kg bw/d with an increase in does found dead, sacrificed in extremis or sacrificed following abortion. Clinical signs consisted of lateral position, poor general state, abortion, blood in bedding, discoloured or no urination and no or reduced defecation at 600 mg/kg bw/d. At the same dose, food consumption was decreased (8%), though there was no effect on body weight or body weight gain. At necropsy, there were increases (1-3/17-23 dams) in stomach ulceration and no faeces in the intestines at doses ≥ 200 mg/kg bw/d and in pale livers and kidneys, empty stomachs and enlarged bladders (1-3/17) at 600 mg/kg bw/d. Platelet counts were significantly decreased (12%) at 600 mg/kg bw/d, serum gamma glutamyl transferase activity was significantly decreased (19-20%), and triglycerides were increased (13-20%) at doses ≥ 200 mg/kg bw/d. Total bilirubin were increased (6-11%) and total liver porphyrins were increased (5-28-fold) at doses >50 mg/kg bw/d. There were no treatment-related adverse changes in organ weight. Gravid uterine weights were decreased (8%) at 600 mg/kg bw/d along with decreased corpora lutea (10%), implantations (10%), live foetuses (11%) and litters (32%). The maternal LOAEL was 600 mg/kg bw/d due to mortality and increased necropsy findings. The NOAEL was 200 mg/kg bw/d.

The only effect on foetal development was an increase in liver porphyrins at 200 mg/kg bw/d.

The developmental LOAEL is 200 mg/kg bw/day, based on increased liver porphyrins. The developmental NOAEL is 50 mg/kg bw/day.

The developmental toxicity study in the rabbit is classified acceptable, guideline and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbit.

A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID 47128117) BAS 800H (93.8% a.i., batch/lot # COD-000515) was administered to 25 Wistar rats/sex/dose in the diet at nominal dose levels of 0, 5, 15, or 50 mg/kg bw/day. Dietary concentrations were varied based on food consumption and body weight in order to maintain a constant dosage throughout treatment.

In F0 and F1 parental generations, no treatment-related effects were observed on mortality, clinical observations, estrous cycle length and periodicity, sperm measures, or gross and microscopic pathology. Mean body-weight gain in high-dose F0 females was statistically significantly decreased on gestation days 7-20 (11-19%) and days 1-4 of lactation (55%). Mean body weights of high-dose F1 males were statistically significantly lower (10%) from week 5 onwards until the end of the study. Mean body weight gain of high-dose F1 males was

statistically significantly decreased on a number of occasions during the treatment period. For the entire dosing period (weeks 0–15), mean body weight gain of high-dose males was approximately 11% lower than the concurrent control value. Mean body weights of F1 females at 50 mg/kg bw/d were statistically significantly lower (6%) than control females on gestation day 20. Mean body weight gain was statistically significantly lower in these females on gestation days 14-20 (21%) and 0-20 (12%). At the beginning of lactation (days 1-4), high-dose F1 females still had significantly lower weight gain (-49%) when compared to the concurrent control, but recovered afterwards. Food consumption of high-dose F1 males was decreased (<10%) during premating. Food consumption of high-dose F1 females was decreased during pre-mating weeks 4-7 (<10%) and during lactation days 1-14 (<26%). Hemoglobin concentrations and other hematological parameters (Hct, MCV, MCH, and/or MCHC) were decreased up to 16% in both sexes of the F0 and F1 generations at 50 mg/kg bw/d. Serum triglyceride levels were also decreased (≤32%) in high-dose males of both F0 and F1 generations; however, the toxicological significance of this decrease is unknown. Increased absolute and relative spleen weights were observed in high-dose F0 and F1 males, a finding that was consistent with the anemia observed in these animals.

The parental systemic LOAEL is 50 mg/kg bw/day, based on decreased body weight, body weight gain, food consumption, and changes in hematological parameters and organ weights indicative of anemia. The parental systemic NOAEL is 15 mg/kg bw/day.

In F1 and F2 offspring, there were no treatment-related effects on clinical observations, sex ratio, sexual maturation, clinical chemistry, organ weight, or microscopic observations. The number of live born pups was decreased (P<0.01) by both the F0 (240 vs. 283 in controls) and F1 (211 vs. 243 in controls) parental generations at 50 mg/kg bw/day. This was due to an increase (P<0.01) in the number of stillborn pups produced by parental females in both generations and led to a corresponding decrease in the live birth index. The number of pups that died after birth was also increased (P<0.01) at 50 mg/kg bw/day for both F0 (9 vs. 0 in controls) and F1 (12 vs. 1 in controls) parents. Two high-dose F1 parental females had 7 and 2 stillborn pups, respectively, and the remaining 1 and 5 pups of these litters were dead by lactation day 4. Based on pup mortality during weaning, the viability index was decreased (P<0.01) in F1 and F2 pups. The lactation index was also decreased (P<0.01) due to a decrease in the number of F1 pups surviving (172 vs. 199 in controls) from days 4-21. Mean body weights and/or body weight gain were decreased in both F1 (up to 16%) and F2 (up to 22%) pups during the pre-weaning period. Platelet counts were decreased by 33% (P<0.01) in high-dose female F1 pups on PND 4. Platelet counts were also decreased by up to 38% (P<0.01) on PND 4 in high-dose male and female pups of the F2 generation. Hemoglobin and Ht levels were decreased by 20% (P<0.01) and 16% (P<0.05) in high-dose F2 females on PND 4. Mean immature nucleated red blood cells were also increased 3-5-fold on PND 4 in high-dose F1 and F2 males and females, but only attained statistical significance in F2 animals. The increases may have been a compensatory response to the observed anemia in F2 females. Discoloured liver was observed in 3 animals from 2 litters in the F1 generation and 5 animals from 4 litters in the F2 generation. Although the liver can be a target of toxicity due to porphyrin accumulation with this compound, this finding was considered treatment-related but not toxicologically significant in the absence of any other indications of hepatotoxicity.

The offspring and reproductive LOAEL is 50 mg/kg bw/day, based on decreased number of live born pups, increased number of stillborn pups, decreased viability and lactation indices,

decreased pre-weaning body weight and/or body weight gain, and changes in hematological parameters. The offspring and reproductive NOAEL is 15 mg/kg bw/day.

This study is acceptable (guideline) and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800); OECD 416 in rat.

870.4100b Chronic Toxicity - Dog

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 47128118), BAS 800 H (93.8%) was administered daily via gelatin capsules to purebred Beagle dogs, 5/sex/group, at nominal doses of 0, 5, 20, or 80 mg/kg bw/d for one year.

There were no treatment-related effects on mortality, ophthalmoscopy, urinalysis, organ weight, or gross pathology. Signs of systemic toxicity were evident at 80 mg/kg bw/d only. At this dose level, oral exposure to BAS 800 H led to discolored feces, lower mean corpuscular volume (MCV, 10-16%) and MCH concentration (11-18%), increased serum alkaline phosphatase activity (45-252%), lowered total blood protein (5-7%) and albumin (5-13%) levels. A slightly more pronounced iron storage in Kupffer cells and hepatocytes was also observed.

The LOAEL was 80 mg/kg bw/d based on decreased albumin, total protein, MVH, and MCH and the NOAEL was 20 mg/kg bw/d.

This chronic study in the dog is acceptable, guideline and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dogs.

A.3.5 Carcinogenicity

870.4200a Carcinogenicity Study – rat

EXECUTIVE SUMMARY: In a combined 2-year toxicity and carcinogenicity study (MRID 47128120), BAS 800 H (93.8%) was administered in the diet to Wistar rats (50/sex/group; satellite groups of 10/sex) at nominal concentrations of 0, 20, 100, 250 (♂), 500 or 1000 (♀) ppm (♂ = 0, 0.9, 4.8, 12.0, 24.2; ♀ = 0, 1.3, 6.2, 31.4, 63.0 mg/kg bw/d, respectively) for 24 months. The satellite groups were dosed for 12 months.

Dietary exposure to BAS 800 H had no adverse effects on mortality, food consumption, food efficiency, body weight, body weight gain, ophthalmoscopy, serum enzyme activity, clinical chemistry, organ weights, gross or histopathology. The satellite rats exhibited signs of general systemic toxicity as well as anemia. General systemic toxicity was observed in rats exposed for 24 months, as evidenced by an increased incidence of smeared anogenital region in females at 500 and 1000 ppm. Anemia was the most conspicuous finding, which was evidenced by a slight decrease of the hemoglobin (3-9%) and/or Ht (4-6%) values and/or lower MCV and MCH (3-8%) indices in males and females at 500 ppm, and in females at 1000 ppm. The biochemical target of BAS 800 H was the protoporphyrinogen IX oxidase enzyme. There were no treatment-related increased incidences of neoplastic findings at any dietary concentrations.

The LOAEL for systemic toxicity was 1000 ppm for female rats (♀ = 31.4 mg/kg bw/d) based on decreased hemoglobin, Ht, MCV and MCH. The NOAEL was 500 ppm for female rats (♀ =

6.2 mg/kg bw/d). The NOAEL for males was 500 ppm (♂ = 24.2 mg/kg bw/d). A LOAEL was not established.

There was no evidence of carcinogenicity.

The doses selected for this study were recommended by the HED Dose Adequacy Review Team (DART). Although, systemic toxicity was not observed in male rats at the highest dose tested, this study should be acceptable based on the toxicity seen in the 28 day and the 90-day studies (DART, PC code 118203)."

Therefore, this chronic/carcinogenicity study in the rat is acceptable/guideline and satisfies the guideline requirement for a chronic/ carcinogenicity study [(OPPTS 870.4300); OECD 453] in rats.

870.4200b Carcinogenicity (feeding) - Mouse

EXECUTIVE SUMMARY: In a oncogenicity study (MRID 47128119), BAS 800 H (93.8%) was administered daily in the diet to groups of C57BL/6NCrl mice, 50/sex/group at nominal doses of 0, 1 (♂), 5, 25, 75, or 150 (♀) ppm (♂ = 0, 0.2, 0.9, 4.6, 13.8; ♀ = 0, 1.2, 6.4, 18.9, 38.1 mg/kg bw/d, respectively) for 18 month. In satellite groups of 10 mice/sex/group, BAS 800 H was administered daily in the diet at 0, 75 (♂), and 150 (♀) ppm (♂ = 0, 14.2; ♀ = 0, 39.0 mg/kg bw/d, respectively) over a period of ten months.

There were no treatment-related effects on mortality, body weight and body-weight gain, food consumption and food efficiency, gross pathology, or organ weights. Treatment induced systemic toxicity was evident at the high dose males (75 ppm) and females (150 ppm) only. The effects included anemia (6-8% decrease in red blood cells, hemoglobin, and Ht) and increased total fecal (27-28%) and liver porphyrin (28-102%) levels (assessed in satellite animals only).

The lowest-observed-adverse-effect levels (LOAELs) in male and female mice were 75 ppm (13.8 mg/kg bw/d) and 150 ppm (38.1 mg/kg bw/day), respectively, based on decreased red blood cells, hemoglobin, and Ht and porphyria observed in the satellite group. The no-observed-effect-levels (NOAELs) were 25 ppm (4.6 mg/kg bw/d) in males and 75 ppm (18.9 mg/kg bw/d) in females. BAS 800 H was not carcinogenic at the dose levels tested.

There was no evidence of carcinogenicity.

This chronic/carcinogenicity study in mice is acceptable/guideline and satisfies the guideline requirement for a chronic/ carcinogenicity study [(OPPTS 870.4300); OECD 453] in mice.

A.3.6 Mutagenicity

Gene Mutation

870.5100, *In vitro* Bacterial Gene Mutation MRID 47128121 Acceptable/guideline	0, 55, 174, 550, 1740, or 5500 ug/plate in the presence and absence of mammalian metabolic activation in the standard plate test and pre-incubation test. Negative for inducing gene mutations in *S. typhimurium* strains TA 1535, TA1537, TA1538, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA up to 5000 µg/plate (limit concentration) in the absence and presence of metabolic activation.

870.5100, *In vitro* Bacterial Gene Mutation MRID 47128122 Acceptable/guideline	0, 20, 100, 500, 2500, or 5000 ug/plate in the presence and absence of mammalian metabolic activation in the standard plate test and pre-incubation test. Negative for inducing gene mutations in *S. typhimurium* strains TA 1535, TA1537, TA1538, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA up to 5000 µg/plate (limit concentration) in the absence and presence of metabolic activation.

Cytogenetics

870.5300, *In Vitro* Mammalian Cells in Culture Gene Mutation assay in Chinese Hamster ovary (CHO) Cells (HPRT Locus Assay); MRID 47128123 Acceptable/guideline	0, 312.5, 625, 1250, 2500, or 5000 µg/mL with and without metabolic activation. There was no evidence of induced mutant colonies over background.
870.5300, *In Vitro* Mammalian Cells in Culture Gene Mutation assay in Chinese Hamster V79 Cells (HPRT Locus Assay); MRID 47128124 Acceptable/guideline	In the first assay, 0, 156.25, 312.5, 625, 1250, 2500, or 5000 µg/mL with and without metabolic activation. In a second assay, 0, 250, 500, 1000, 2000, or 4000 µg/mL without metabolic activation or 0, 1000, 2000, or 4000 µg/mL with metabolic activation. In a third assay, 0, 500 (+S9 only),1000, 2000, 3000, 4000, or 5000 (-S9 only) µg/mL with or without S9 activation. Clastogenic in *Chinese hamster V79 cells* in the presence of metabolic activation tested up to the limit concentration, 5000 ug/mL. BAS 800 H was not clastogenic in the absence of metabolic activation.

Other Genotoxicity

870.5395, *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in mice MRID 47128125Acceptable/guideline	500, 1000 and 2000 mg/kg body weight Negative for the increase in frequency of micronucleated immature erythrocytes in mouse bone marrow tested up to 2000 mg/kg (limit dose).
870.5550, Unscheduled DNA Synthesis in Primary Rat Hepatocytes/Mammalian Cell Cultures MRID 47128126 Acceptable/non-guideline	1,000 or 2,000 mg/kg body Negative for inducing unscheduled DNA synthesis in Wistar rat primary hepatocytes tested up to 2000 mg/kg (limit dose).

A.3.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 47128127), BAS 800 H (93.8% a.i.) in aqueous 0.5% carboxymethylcellulose was administered to Wistar rats, 10/sex/group, by oral gavage at 0, 125, 500, or 2000 mg/kg bw. The rats were observed for two weeks. Neurobehavioral assessment (functional observation battery and motor activity testing) was performed on days -7, 0, 7, and 14. At study termination, 5 rats/sex/group were euthanized and perfusion fixed for neuropathological examination.

All rats survived the duration of the study period. There were no treatment-related effects on clinical signs of toxicity, food consumption and food efficiency, body weights and body-weight gain, or FOB. The only noted finding was a moderately decreased motor activity in high-dose males. The finding was not accompanied by any other neuropathological changes and was considered to be a reflection of a mild and transient general systemic toxicity and not a

substance-specific neurotoxic effect. At terminal sacrifice, the brain weight was not affected. Gross and histopathological examination of the brain or other nervous tissues revealed no treatment-related changes. For systemic toxicity, the LOAEL was 2000 mg/kg bw for the males based on the decreased motor activity. The LOAEL for the female was not observed. The systemic toxicity NOAELs for the male and female rats were 500 and 2000 mg/kg bw, respectively.

This acute neurotoxicity toxicity study in the rat is an acceptable guideline study and satisfies the guideline requirement for an acute oral toxicity study (OPPTS 870.6200a; OECD 424) in the rat.

870.6200 Subchronic Neurotoxicity Screening Battery

EXECUTIVE SUMMARY: In a 90-day oral neurotoxicity study (MRID 47128128), Wistar rats (10/sex/group) were administered BAS 800 H (purity 93.8 %) daily in the diet at nominal doses of 0, 50, 250, 1000 (♂), or 1350 (♀) ppm (♂ = 0, 3.3, 16.6, 66.2; ♀ = 0, 3.9, 19.4, 101.0 mg/kg bw/d, respectively). Neurobehavioral assessment (functional observation battery and motor activity testing) was performed on days -7, 1, 22, 50, and 85. At study termination, 5 rats/sex/group were euthanized and perfusion fixed. The brain and other nervous tissues were processed for histopathologic examination.

There were no mortalities. At the top dose levels (♂ = 1000, ♀ = 1350 ppm), treatment-related systemic toxicity was evident in both sexes. The effects included decreased food consumption (6-14%), decreased body weight (5-9%) and body-weight gain (14-16%), decreases in hematological values (hemoglobin, 10-13%; Ht, 9% in males; mean corpuscular volume, 10-11%; MCH, 13-14%; and MCHC, 4-5%). The hematological effects were evidence of anemia. Neurotoxicity assessment including an extensive functional observational battery, motor activity, brain weights, as well as gross and histopathology of the brain and other nervous tissues did not reveal any adverse findings.

The LOAELs for general systemic toxicity for the male and female were 1000 and 1350 ppm, respectively (♂ = 66.2, ♀ = 101.0 mg/kg bw/d) based on decreased hemoglobin, Ht, mean corpuscular volume and MCH. The NOAEL for systemic toxicity was 250 ppm (♂ = 16.6, ♀ = 19.4 mg/kg bw/d).

The study is classified as acceptable guideline and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b).

A.3.8 Metabolism

870.7485 Metabolism - Rat

EXECUTIVE SUMMARY: In a metabolism study (MRID 47128130) BAS 800 H (100% a.i.), [phenyl-U-14C]-BAS 800 H (>95.0% radiochemical purity) was administered to 4 Wistar rats/sex/group via gavage at 4, 20, or 100 mg/kg bw for plasma kinetics and 5 or 100 mg/kg bw for mass balance, tissue distribution and biliary excretion experiments.

After a single oral administration of 100 mg/kg bw of 14C-BAS 800 H, mean total recoveries of radioactivity were >90% in both sexes. In exhaled air, no administered radioactivity (AR) was excreted as CO2. After 168 h, the total amounts of radioactivity excreted in urine were 52.6 and

86.6% in males and females, respectively. In feces, 43.3 and 9.8% of AR were recovered in males and females, respectively. The time course of the amount of radioactivity found in urine and feces indicated rapid excretion.

With repeat dosing (14 oral applications with unlabelled BAS 800 H at 100 mg/kg bw and one oral application with labelled 14C-BAS 800 H at 100 mg/kg bw), a similar pattern of excretion was also seen. After 168 h, the total amounts of radioactivity excreted in urine were 67.8 and 83.4% in males and females, respectively. In feces, 35.8 and 13.4% of AR were recovered in males and females, respectively.

After single oral administration of 5 mg/kg bw, mean total recoveries of radioactivity were >90% in males and females. No AR was excreted as CO2 in exhaled air. Within 168 h 26.0 and 96.1% of AR were excreted in urine of male and female rats, respectively. In feces, 81.2 and 12.8% AR were recovered in males and females, respectively. The time course of the amount of radioactivity found in urine and feces indicated rapid excretion. The results demonstrated a sex-specific excretion pattern for 14C-BAS 800 H with a higher amount of urinary excretion for females than for males. This sex difference was more pronounced at the low dose level than at the high dose level.

A comparable time course of radioactivity was found for blood and plasma in both sexes. A relatively constant blood/plasma ratio was generally found with the observation period of 168 h, indicating that majority radioactivity was in plasma and not bound to cellular blood constituents.

The AUC values for doses of 14C-800 H of 4, 20, and 100 mg/kg bw were 741, 2131, 4502 [µg Eq × h/g] for males and 247, 754, and 3057 [µg Eq × h/g] for females. The findings indicated a sex difference with up to three fold higher internal exposures for males than for females. Increasing the dose by a factor of 25 resulted in an increase of the AUC-values by a factor of 6.1 in males and 12.4 in females. These data indicated a sub-linear correlation of the internal exposure with increasing internal dose.

After a single oral dose of 14C-BAS 800 H at 5 or 100 mg/kg bw, analyses of radioactivity in tissues indicated higher levels in males than in females at respective time points and dose levels, whereas the pattern of distribution in the various organs and tissues was similar in both sexes. Tissue radioactivity concentrations generally declined with time parallel to plasma concentrations. Throughout the time course of the experiments, highest radioactivity levels were generally found in the GI tract, liver, kidneys, lungs, and thyroid whereas radioactivity levels were lowest in brain and bone. Similar findings were noted with repeat dosing.

Within 48 h of administration of 14C-BAS 800 H, excretion of radioactivity in the bile in males and females was 52.3 and 18.9% and 67.8 and 35.5% AR at 5 and 100 mg/kg bw dose levels, respectively. The data indicated higher biliary excretion in males when compared to females.

In conclusion, the biokinetics data demonstrated that orally administered BAS 800 H was rapidly absorbed, distributed, and excreted. Regardless of the dose administered, maximum concentration of BAS 800 H in blood and plasma was reached within 1 h of dosing and declined rapidly after 24 h. The blood and plasma data demonstrated that the majority of the BAS 800 H residues occurred in the plasma and was not bound to cellular elements of the blood. There was a sex dependent difference in the excretion of orally administered BAS 800 H. Following single low- and high-dose administration or a repeat high-dose administration, the main route of

elimination in male rats was via the feces, while urinary excretion was the major route of elimination in females. The sex dependent excretion was more pronounced at the low dose level than at the high dose level. The sex dependent difference in excretion of orally dosed BAS 800 H was also demonstrated by the biliary excretion data which showed significantly higher biliary excretion of BAS 800 H residues in males than in females. Excretion of orally dosed BAS 800 H was essentially complete within 96 h, the majority was eliminated within the first 24 to 48 h. Exhalation was not a relevant excretion pathway of BAS 800 H. At 168 h after dosing, BAS 800 H residues remaining in tissues were very low, and occurred mainly in carcass, liver, skin, and gut contents.

Studies of the metabolic pattern and identification on metabolites in the rats indicated that BAS 800 H was metabolized by three major transformation steps, which were demethylation of the uracil ring system, degradation of the N-methyl-N-isopropyl group to NH2, and cleavage of the uracil ring, forming a sulfonylamide group. The predominant metabolites were M800H01, M800H03, M800H07 and the parent compound. Other minor metabolites were M800H05, M800H16, M800H17, M800H18, M800M19, and M800M20. There were no significant gender differences in metabolic profiles.

This metabolism study in the rat is classified acceptable, guideline and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

870.7600 Dermal Absorption - Rat

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 47128214) BAS 800 02H in the formulation concentrate (93.3 % 14C-BAS 800 H., batch/lot #825-1401) was administered to Crl: WI (HAN) male Wistar rats 4/dose to the dorsal area at dose levels of 1.1723 mg/cm2, 0,1172 mg/cm2 and 0.0117 mg/cm2 (corresponding nominally to about 11.723, 1.172 and 0.117 mg/animal and about 36.9, 4.0 and 0.4 mg/kg body weight). Exposure duration was 10 hours and animals were monitored for 10, 24, 72 and 120 hours.

Mean recoveries of radioactivity from all dose groups were in the range of 92.00% to 115.20% of the total radioactivity administered. The largest proportion of radioactivity was recovered from the carcass and the feces samples from the high-dose group and in the skin washes of the mid- and low-dose groups.

At the high-dose, the formulation concentrate, a systemic absorption (including skin bound residues) of about 72.03% was observed after a 10 h exposure period to BAS 800 H. At sacrifice after 120 h, the absorption was 82.55% of the dose. In the high-dose group, about 2/3 of the radioactivity remaining in the skin after the end of exposure penetrated through the skin during the 5- day post-observation period.

At the mid-dose, a 1/10 aqueous dilution of the formulation concentrate, a systemic absorption of about 2.78% was observed immediately after a 10 h exposure period to BAS 800 H. At sacrifice after 24, 72 and 120 h, the absorptions were 3.96, 8.57 and 3.36%, respectively. In the mid-dose group, about 50% of the radioactivity remaining in the skin after the end of exposure penetrated through the skin during the 5- day post-observation period.

At the low-dose, i.e. a 1/100 aqueous dilution of the formula concentrate, a systemic absorption of about 3.39% was observed immediately after a 10 h exposure period for BAS 800 H. At

sacrifice after 24, 72 and 120 h the absorptions were 4.80, 4.01 and 5.94% of the radioactivity applied, respectively. In the low-dose group, about 50% of the radioactivity remaining after the end of exposure penetrated through the skin during the 5- day post-observation period. The highest tissue concentrations of radioactivity were generally found in plasma and carcass.

This study in the rat is acceptable, guideline and satisfies the guideline requirement for a dermal penetration study (870.7600) in rats.

A.3.9 Special/Other Studies

Total porphyrin analysis in rat; Non-guideline

EXECUTIVE SUMMARY: In a repeat-dose mechanistic toxicity study (MRID 47128132), BAS 800 H (94.2%) was administered in the diet to groups of Wistar rats, 10/sex/group, at nominal doses of 0, 10, 50, or 1000 ppm (♂ = 0, 0.8, 4.1, 80.6; ♀ = 0,, 0.9, 4.6, 89.5 mg/kg bw/d, respectively) for an eight week period. A two-week recovery period was maintained for five animals per sex/group. The effects of BAS 800 H administration on porphyrin levels in plasma, urine, feces, and liver were monitored.

Dietary administration of BAS 800 H at 1000 ppm caused a moderate microcytic hypochromic anemia (sideroblastic anemia) due to inhibition of heme biosynthesis. The inhibition of protoporphyrinogen IX oxidase resulted in increased accumulation and excretion of large amounts of porphyrins and their precursors resulting in marked porphyria. Animals treated with lower concentrations of BAS 800 H showed no signs of anemia. At 1000 ppm, anemia was observed in both sexes. However, at 50 ppm, BAS 800 H still caused significant porphyria in male and female rats. Small, but statistically significant, increases in porphyrin levels in urine of males and in feces of both sexes at 10 ppm were still noted. In general, the total porphyrin concentrations in the plasma, urine, feces, and liver were statistically significantly increased in male and female rats at 50 and 1000 ppm.

Both individual porphyrin (HPLC) and total porphyrin (spectroflurometric) measurements were made to assess correlation of the two methods. The results indicated a strong correlation and both types of measurements provided reliable dose-response information regarding protoporphyrinogen IX oxidase inhibition. Total porphyrins in feces and liver provided the most reliable and sensitive data. Statistically significant effects on porphyrin metabolism could be detected at exposure concentrations well below those associated with adverse hematological effects.

As effects on porphyrins were seen at 10 ppm, the NOEL for porphyrin effects was <10 ppm. The LOAEL is 1000 ppm (M/F: 80.6/89.5 mg/kg bw/d) based on anemia. The NOAEL is 50 ppm (M/F: 4.1/4.6 mg/kg bw/d).

This study in the rat is classified acceptable/non-guideline.

Porphyrin analysis supplementary- rat;Non-guideline

EXECUTIVE SUMMARY: In a repeat-dose mechanistic toxicity study (MRID 47128131), BAS 800 H (94.2%) was administered in the diet to groups of Wistar rats, 10/sex/group, at 0, 1, 5, or 25 ppm (♂ = 0, 0.1, 0.4, 2.0; ♀ = 0, 0.1, 0.5, 2.3 mg/kg bw/d, respectively) for an eight

week period. The rats were examined for signs of toxicity and mortality twice a day. Body weights and food consumption were determined once a week. Blood and feces from all rats were sampled after 1, 2, 4, and 8 weeks of BAS 800 H treatment. Hematological examinations were performed and total porphyrin concentrations in feces were measured. At study termination, all rats were sacrificed under CO2 anesthesia and assessed for gross pathological changes.

There were no adverse effects of treatment on mortality, clinical observation, body weight, food consumption or hematological parameters. Dietary administration of BAS 800 H at 25 ppm caused an increase in porphyrin in feces of male (237%) and female (61%) rats, while BAS 800 H at 5 ppm caused an increase (127%) in fecal porphyrin only in males. At 1 ppm, there were no effects on porphyrin excretion in the feces.

This study in the rat is classified **acceptable/non-guideline**.

Comparative Bioavailability/Toxicity Study-rat; Non-guideline

EXECUTIVE SUMMARY: BAS 800 H-hydrate (93.9%) or BAS 800 H-anhydrate (99.0%) (MRID 47128133) were administered to groups of 10 male Wistar rats at dietary concentrations of 0 or 1350 ppm over a period of 4 weeks in order to determine if there are toxicologically significant differences between the two different crystalline forms of BAS 800 H. After dosing, the rats were examined for signs of toxicity or mortality twice a day. Body weights were determined on day 0, then weekly thereafter. Food consumption was recorded weekly. Feces and blood from all rats were sampled on days 14 and 28 for hematological and porphyrin determinations. At study termination, all rats were sacrificed under CO2 anesthesia and assessed for gross pathological changes. The weights of the spleen and liver were recorded. The livers were also analyzed for porphyrin concentrations. The results indicated very similar effects following dietary exposure to the hydrated or anhydrate form of BAS 800 H. The effects included impairment of food intake (7-10%); significant decreases in erythrocyte counts (2-13%), hemoglobin (21-29%), Ht (16-20%), mean corpuscular volume (8-14%), MCH (8-24%), MCHC (6-11%); increased reticulocyte (196-311%) and platelet counts (8-17%); increases in porphyrin levels in the liver (~24-fold) and feces (~14-17-fold); and increases in absolute and relative spleen weights (70-125%). Based on the similarity of the findings, it was concluded that the bioavailability and toxicity potential of the hydrated and anhydrated form of BAS 800 H were similar.
This study in the rat is classified acceptable/non-guideline.

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Appendix B: Metabolism Assessment

B.1. Metabolism Guidance and Considerations

Table B.1.1. Tabular Summary of Metabolites and Degradates.

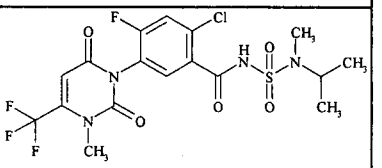
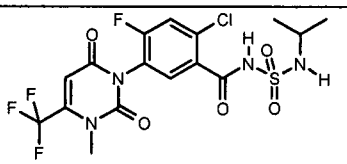
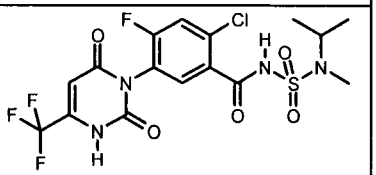
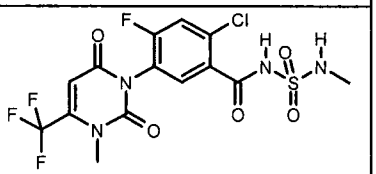
Chemical Name (other names in parenthesis)	Matrix	Percent TRR[1]		Structure
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)	
Saflufenacil (2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluoro-*N*-[[methyl(1-methylethyl)amino] sulfonyl]benzamide)	Plants	Soybean forage; Tomato plant	Soybean seed, pod, straw; Tomato fruit; Corn husks, stover, forage	
	Rotational Crops	Lettuce; Radish top	Wheat forage	
	Ruminant	Muscle, Fat, Liver, Kidney, Milk	-	
	Poultry	Muscle, Eggs, Fat, Liver	-	
	Rat	Urine, Feces, Bile, Fat, Liver, Kidney, Plasma		
	Water			
M800H01 (*N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropylsulfamide*)	Plants	Corn forage	Soybean forage, seed, straw, pod; Tomato plant	
	Rotational Crops	Radish top; Lettuce	Wheat forage, grain, chaff, straw	
	Ruminant	-	Liver, Kidney, Milk	
	Poultry	Liver	Muscle, Eggs, Fat	
	Rat	Urine, Feces, Bile	Fat, Liver, Kidney, Plasma	
	Water	Aerobic soil		
M800H02 (*N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-N-isopropyl-N-methylsulfamide*)	Plants	Soybean forage	Soybean seed, straw, pod; Corn forage; Tomato plant	
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	Muscle, Liver, Fat	
	Rat		Urine, Feces, Bile	
	Water	Aerobic soil		
M800H03 (*N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-methylsulfamide*)	Plants	Corn, forage	Soybean forage; Corn, stover	
	Rotational Crops	-	Radish top; Lettuce; Wheat forage, grain, chaff, straw	
	Ruminant	-	Kidney, Milk	
	Poultry	-	Muscle, Liver	
	Rat		Urine, Feces, Liver, Kidney	
	Water	-	-	

Table B.1.1. Tabular Summary of Metabolites and Degradates.

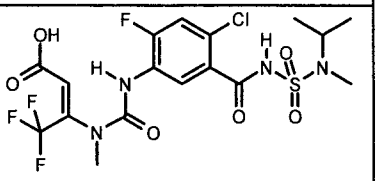
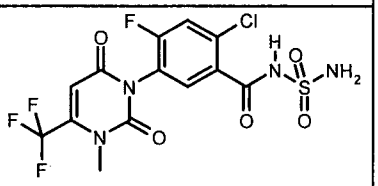
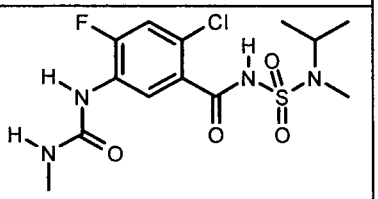
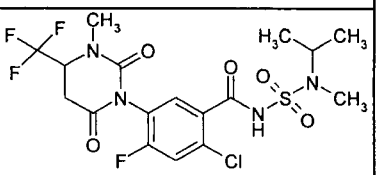
Chemical Name (other names in parenthesis)	Matrix	Percent TRR[1]		Structure
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)	
M800H04 *((2E)-3-{4-chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino)carbonyl]phenyl)amino]carbonyl(methylamino)}-4,4,4-trifluorobut-2-enoic acid)*	Plants	-	-	
	Rotational Crops	-	-	
	Ruminant	Liver, Kidney	-	
	Poultry	-	-	
	Rat	Liver, Kidney	Urine, Feces, Fat, Plasma	
	Water		Aq. photolysis - pH5, Hydrolysis, Anaerobic water	
M800H05 *(N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-sulfamide)*	Plants	Corn forage	Soybean seed, straw; Corn husks	
	Rotational Crops	Wheat forage, chaff, straw	Wheat grain	
	Ruminant	-	-	
	Poultry	-	Muscle, Eggs, Fat, Liver	
	Rat		Urine, Feces	
	Water	-	-	
M800H07 *(N-{4-chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino)carbonyl]phenyl}-N'-methylurea)*	Plants	-	-	
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	-	
	Rat	Bile	Urine, Feces, Kidney, Plasma	
	Water	Aerobic soil, Soil photolysis, Aq. Photolysis –pH7, Hydrolysis –pH9, Aerobic water, Anaerobic water, Field studies		
M800H08 *(N'-[2-Chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl) tetrahydro-1(2H)-pyrimidinyl) benzoyl]-N-isopropyl-N-methylsulfamide)*	Plants	-	-	
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	-	
	Rat	-	-	
	Water	Aerobic soil, Soil photolysis, Field studies		

Table B.1.1. Tabular Summary of Metabolites and Degradates.

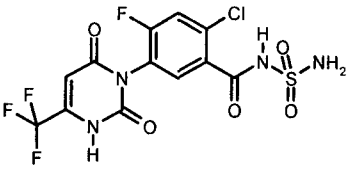
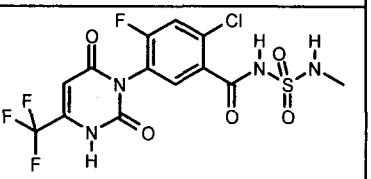
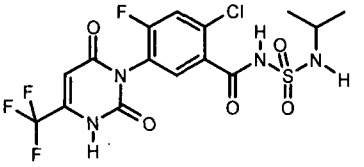
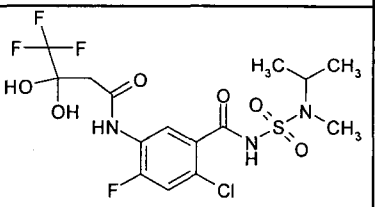
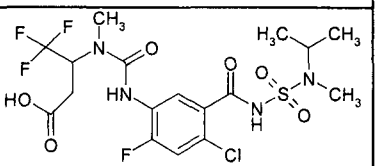
Chemical Name (other names in parenthesis)	Matrix	Percent TRR[1]		Structure
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)	
M800H09 *(N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-sulfamide)*	Plants	Corn stover	Corn husks, cob, forage, grain; Tomato plant[2]	
	Rotational Crops	See M800H35		
	Ruminant	-	-	
	Poultry	-	-	
	Rat		Urine, Feces	
	Water	-	-	
M800H10 *(N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-N-methylsulfamide)*	Plants	Soybean seed[3], straw[3], pod[3]; Corn stover	Soybean forage[3]; Corn forage, husks, cob; Tomato plant	
	Rotational Crops	Radish top[4]; Wheat forage[4], chaff[4], straw[4]	Lettuce[4]; Wheat grain[4]	
	Ruminant	Muscle, Fat, Milk	Liver	
	Poultry	Muscle, Eggs, Fat	Liver	
	Rat	-	-	
	Water	-	-	
M800H11 *(N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-N-isopropylsulfamide)*	Plants	Soybean straw; Tomato plant	Soybean forage, seed, pod; Corn forage, husks, cob,stover	
	Rotational Crops	Radish top	Lettuce; Wheat forage, grain, straw	
	Ruminant	-	-	
	Poultry	-	Muscle, Eggs, Fat, Liver	
	Rat	-	-	
	Water	-	-	
M800H15 *(N-{4-Chloro-2-fluoro-5-[({[isopropyl (methyl) amino] sulfonyl} amino) carbonyl] phenyl}-4-4-4-trifluoro-3,3-dihydroxybutanamide)*	Plants	-	-	
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	-	
	Rat	-	-	
	Water	Hydrolysis –pH9, Anaerobic water		
M800H22 *(3-[({4-Chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino)carbonyl]anilino }carbonyl)(methyl)amino]-4,4,4-trifluorobutanoic acid)*	Plants	-	-	
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	-	
	Rat	-	-	
	Water	Aerobic soil		

Table B.1.1. Tabular Summary of Metabolites and Degradates.

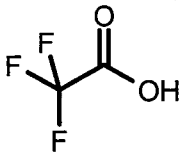
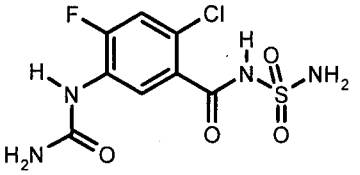
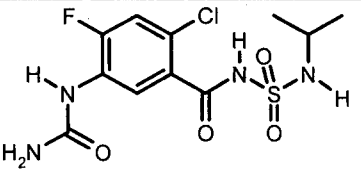
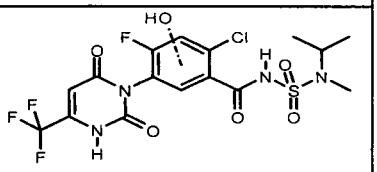
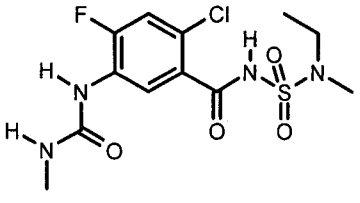
Chemical Name (other names in parenthesis)	Matrix	Percent TRR[1]		Structure
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)	
M800H29 (TFA) (Trifluoroacetic Acid)	Plants	Soybean forage, seed, straw, pod; Corn husks, cob, grain, forage, stover; Tomato plant, fruit		
	Rotational Crops	Radish root, top; Lettuce; Wheat forage, grain, chaff, straw		
	Ruminant	-	-	
	Poultry	-	-	
	Rat	-	-	
	Water	Aq. Photolysis – pH7, Aerobic water, Anaerobic system		
M800H34 N-{4-chloro-2-fluoro-5-[([aminosulfonyl]amino)carbonyl] phenyl}-N'-methylurea	Plants	Corn cob, stover, forage	Corn husks, grain	
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	-	
	Rat	-	-	
	Water	-	-	
M800H35 (*N*-[4-chloro-2-fluoro-5-({[(isopropylamino) sulfonyl]amino} carbonyl)phenyl] urea)	Plants	Soybean straw, pod	Soybean forage, seed; Tomato plant	
	Rotational Crops	Wheat forage[1], grain[1], chaff[1], straw[1]	Radish top[1]; Lettuce[1]	
	Ruminant	-	-	
	Poultry	-	-	
	Rat	-	-	
	Water	-	Aerobic soil	
M800H36 (Hydroxylated derivative of M800H02)	Plants	See M800H10		
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	-	
	Rat			
	Water	-	-	
M800H37 (N-{4-chloro-2-fluoro-5-[({[ethyl(methyl)amino]sulfonyl}amino) carbonyl]phenyl}-N'-methylurea)	Plants		Soybean forage	
	Rotational Crops	-	-	
	Ruminant	-	-	
	Poultry	-	-	
	Rat	-	-	
	Water	-	-	

Table B.1.1. Tabular Summary of Metabolites and Degradates.

Chemical Name (other names in parenthesis)	Matrix	Percent TRR[1]		Structure
		Matrices - Major Residue (>10% TRR)	Matrices - Minor Residue (<10% TRR)	
Corn, 47128001; 0.169-0.196 lb ai/A; 1.5X rate; single pre-emergent spray application. *Soybean, 47128002; 0.132-0.161 lb ai/A; 1.8X rate; single pre-emergent spray application.* *Tomato, 47128003; 0.089 lb ai/A; single pre-emergent spray application.* *Goat; 47128005 & 47128006; 13.4 ppm; 56X MRDB; 8 days; 23 hour PSI* *Hen; 47128007 & 47128020; 12.6 ppm; 47X MTDB; 10 days; 23 hour PSI* *Rotational Crops; 47128017; lettuce, radish, and spring wheat; 1X, applied to bare soil 30-, 58- (lettuce and radish only), 120-, and 365-day PBIs* *Rat Metabolism; 47128129, 47128130; 4, 20, 100 mg/kg oral dose; Wistar; 0- to 3-day depuration.*				

[1] + M800H09

[2] + M800H05[3] + M800H36[4] + Unknown

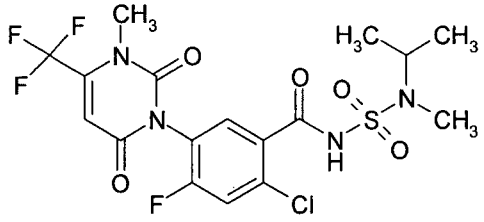
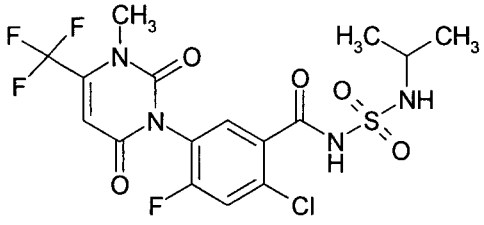
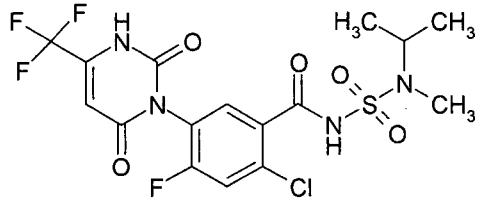
Table B.1.2. Saflufenacil and Its Major Organic Environmental Degradates.					
Code Name/ Synonym	**Chemical Name**	**Chemical Structure**	**Study Type**	**Maximum %AR (day)**	**Final %AR (study length)**
PARENT					
Saflufenacil **BAS 800H**	**IUPAC:** N'-{2-Chloro-4-fluoro-5-[1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)pyrimidin-1-yl]benzoyl}-N-isopropyl-N-methylsulfamide **CAS:** 2-Chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2H)-pyrimidinyl]-4-fluoro-N-[[methyl(1-methylethyl)amino] sulfonyl]benzamide **CAS-no:** 372137-35-4 **Formula:** $C_{17}H_{17}ClF_4N_4O_5S$ **MW:** 500.86 g/mol				
MAJOR (>10%) TRANSFORMATION PRODUCTS					
M01 **M800H01**	N'-[2-Chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N'-isopropylsulfamide **Formula:** $C_{16}H_{15}ClF_4N_4O_5S$ **MW:** 486.83 g/mol		Aerobic soil	**10** (57)	1.3 (330)
			Anaerobic soil	(data submission pending)	
			Soil photolysis	5.4 (14)	nd[1] (30)
			Aqueous photolysis	not detected	
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not detected	
			Anaerobic aquatic	not identified but not major[2]	
			Field studies	0.02 ppm (0-8, 11, 20)	nd[1] (124, 271, 360)
M02 **M800H02**	N'-[2-Chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-N-isopropyl-N-methylsulfamide **Formula:** $C_{16}H_{15}ClF_4N_4O_5S$ **MW:** 486.83 g/mol		Aerobic soil	**30** (246)	17 (330)
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not detected	
			Aqueous photolysis	not detected	
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not detected	
			Anaerobic aquatic	not identified but not major[2]	
			Field studies	0.01 ppm (0-2, 6)	nd[1] (360)

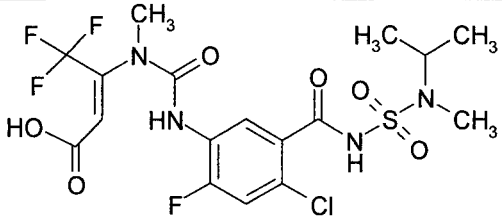
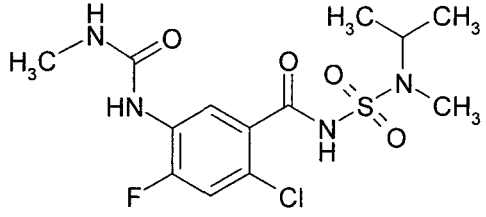
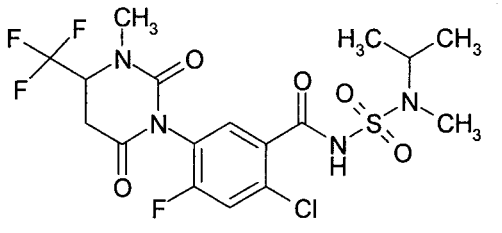
Table B.1.2. Saflufenacil and Its Major Organic Environmental Degradates.					
Code Name/ Synonym	**Chemical Name**	**Chemical Structure**	**Study Type**	**Maximum %AR (day)**	**Final %AR (study length)**
M04 **M800H04**	**Formula:** $C_{17}H_{19}ClF_4N_4O_6S$ **MW:** 518.87 g/mol		Aerobic soil	not identified but not major[2]	
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not identified but not major[2]	
			Aq. photolysis -pH5	5.9 (15)	3.4 (20)
			Aq. photolysis -pH7	not identified	not identified
			Hydrolysis -pH7	0.95 (30)	0.95 (30)
			Hydrolysis -pH9	**13** (3)	nd[1] (30)
			Aerobic aquatic	not identified but not major[2]	
			Anaerobic water	4.4 (62)	nd[1] (364)
			Anaerobic sediment	0.5 (62)	nd[1] (364)
			Anaerobic system	4.4 (62)	nd[1] (364)
			Field studies	not analyzed	
M07 **M800H07**	N-{4-Chloro-2-fluoro-5-[({[isopropyl (methyl) amino] sulfonyl} amino) carbonyl] phenyl}-N'-methylurea **Formula:** $C_{13}H_{18}ClFN_4O_4S$ **MW:** 380.83 g/mol		Aerobic soil	**52** (25)	7.2 (330)
			Anaerobic soil	(data submission pending)	
			Soil photolysis	**19** (14)	2.3 (30)
			Aq. photolysis -pH5	not detected	not detected
			Aq. photolysis -pH7	**13** (21)	13 (21)
			Hydrolysis –pH7	9.2 (30)	9.2 (30)
			Hydrolysis –pH9	77 (30)	77 (30)
			Aerobic water	**20** (30)	19 (60)
			Aerobic sediment	3.7 (60)	3.7 (60)
			Aerobic system	**23** (60)	23 (60)
			Anaerobic water	**62** (364)	62 (364)
			Anaerobic sediment	**13** (91)	6.7 (364)
			Anaerobic system	**71** (91)	68 (364)
			Field studies	0.02 ppm (11, 20, 44)	nd[1] (124, 271)
M08 **M800H08**	N'-[2-Chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl) tetrahydro-1(2H)-pyrimidinyl) benzoyl]-N-isopropyl-N-methylsulfamide **Formula:** $C_{17}H_{19}ClF_4N_4O_5S$ **MW:** 502.88 g/mol		Aerobic soil	**66** (246)	41 (330)
			Anaerobic soil	(data submission pending)	
			Soil photolysis	**19** (22)	18 (30)
			Aqueous photolysis	not detected	
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not detected	
			Anaerobic aquatic	not identified but not major[2]	
			Field studies	0.05 ppm (1, 6)	nd[1] (124, 360)

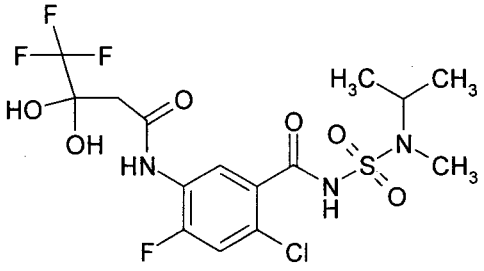
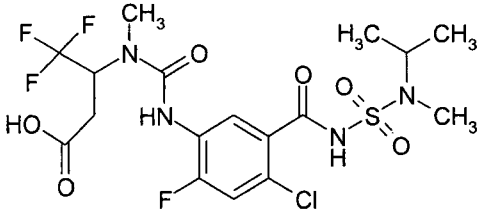
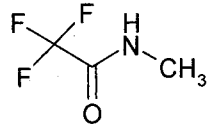
Table B.1.2. Saflufenacil and Its Major Organic Environmental Degradates.					
Code Name/ Synonym	**Chemical Name**	**Chemical Structure**	**Study Type**	**Maximum %AR (day)**	**Final %AR (study length)**
M15 **M800H15**	N-{4-Chloro-2-fluoro-5-[({[isopropyl (methyl) amino] sulfonyl} amino) carbonyl] phenyl}-4-4-4-trifluoro-3,3-dihydroxybutanamide **Formula:** $C_{15}H_{18}ClF_4N_3O_6S$ **MW:** 479.84 g/mol		Aerobic soil	not identified but not major[2]	
			Anaerobic soil	(data submission pending)	
			Soil photolysis	9.6 (30)	9.6 (30)
			Aq. photolysis -pH5	3.0 (20)	3.0 (20)
			Aq. photolysis -pH7	not detected	not detected
			Hydrolysis –pH7	2.3 (30)	2.3 (30)
			Hydrolysis –pH9	**22** (30)	22 (30)
			Aerobic aquatic	not detected	
			Anaerobic water	**17** (62-91)	7.1 (364)
			Anaerobic sediment	0.9 (273)	0.8 (364)
			Anaerobic system	**17** (62-91)	7.6 (364)
			Field studies	not detected	
M22 **M800H22**	3-[({4-Chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino)carbonyl]anilino}carbonyl)(methyl)amino]-4,4,4-trifluorobutanoic acid **Formula:** $C_{17}H_{21}ClF_4N_4O_6S$ **MW:** 520.89 g/mol		Aerobic soil	**16** (43)	7.1 (334)
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not detected	
			Aqueous photolysis	not detected	
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not detected	
			Anaerobic aquatic	not identified but not major[2]	
			Field studies	not detected	
M26 **M800H26**	N-Methyl-2,2,2-trifluoroacetamide **Formula:** $C_3H_4F_3NO$ **MW:** 127.07 g/mol		Aerobic soil	**18** (25)	nd[1] (334)
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not identified but not major[2]	
			Aqueous photolysis	not identified but not major[2]	
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not identified but not major[2]	
			Anaerobic aquatic	not identified but not major[2]	
			Field studies	not analyzed	

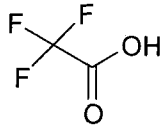
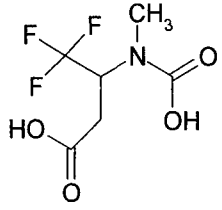
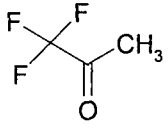
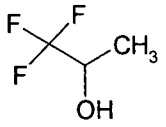
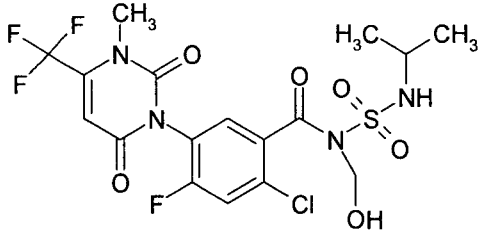
Table B.1.2. Saflufenacil and Its Major Organic Environmental Degradates.					
Code Name/ Synonym	**Chemical Name**	**Chemical Structure**	**Study Type**	**Maximum %AR (day)**	**Final %AR (study length)**
M29 **M800H29** **TFA** **(also formulated as TFA, sodium salt)**	Trifluoroacetic acid **Formula:** $C_2HF_3O_2$ **MW:** 114.02 g/mol		Aerobic soil	not identified but not quantified	
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not identified but not major[2]	
			Aq. photolysis -pH5	4.8 (20)	4.8 (20)
			Aq. photolysis -pH7	**29** (21)	29 (21)
			Hydrolysis	not identified but not major[2]	
			Aerobic water	6.9 (60)	6.9 (60)
			Aerobic sediment	2.0 (51-60)	2.0 (60)
			Aerobic system	8.8 (60)	8.8 (60)
			Anaerobic water	9.2 (364)	9.2 (364)
			Anaerobic sediment	3.6 (91)	1.9 (364)
			Anaerobic system	**11** (364)	11 (364)
			Field studies	not analyzed	
M31 **M800H31**	3-[Carboxy(methyl)amino]-4,4,4-trifluorobutanoic acid **Formula:** $C_6H_8F_3NO_4$ **MW:** 215.13 g/mol		Aerobic soil	**18** (43)	8.7 (334)
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not identified but not major[2]	
			Aqueous photolysis	not identified but not major[2]	
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not identified but not major[2]	
			Anaerobic aquatic	not identified but not major[2]	
			Field studies	not analyzed	
M33 **M800H33**	1,1,1-Trifluoroacetone **CAS-no:** 421-50-1 **Formula:** $C_3H_3F_3O$ **MW:** 112.05 g/mol		Aerobic soil	not identified but not major[2]	
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not identified but not major[2]	
			Aq. photolysis -pH5	not detected	not detected
			Aq. photolysis -pH7	**30** (21)	30 (21)
			Hydrolysis –pH7	4.7 (30)	4.7 (30)
			Hydrolysis –pH9	**74** (21)	73 (30)
			Aerobic water	**23** (7)	3.2 (60)
			Aerobic sediment	nd[1]	nd[1]
			Aerobic system	**23** (7)	3.2 (60)
			Anaerobic water	**15** (62)	nd[1] (364)
			Anaerobic sediment	0.9 (62)	nd[1] (364)
			Anaerobic volatiles	**13** (160-364)	13 (364)
			Anaerobic system	**25** (62)	13 (364)
			Field studies	not analyzed	

Table B.1.2. Saflufenacil and Its Major Organic Environmental Degradates.					
Code Name/ Synonym	**Chemical Name**	**Chemical Structure**	**Study Type**	**Maximum %AR (day)**	**Final %AR (study length)**
TFP	1,1,1-Trifluoro-2-propanol **CAS-no:** 374-01-6 **Formula:** $C_3H_5F_3O$ **MW:** 114.07 g/mol		Aerobic soil	not identified but not major[2]	
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not identified but not major[2]	
			Aqueous photolysis	not identified but not major[2]	
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not identified but not major[2]	
			Anaerobic water	**16** (62)	0.4 (364)
			Anaerobic sediment	3.4 (62)	nd[1] (364)
			Anaerobic volatiles	**24** (160-364)	24 (364)
			Anaerobic system	**30** (62)	24 (364)
			Field studies	not analyzed	
Product 8	**Formula:** $C_{17}H_{15}ClF_4N_4O_6S$ **MW:** 516.86 g/mol		Aerobic soil	not identified but not major[2]	
			Anaerobic soil	(data submission pending)	
			Soil photolysis	**17** (15)	17 (15)
			Aqueous photolysis	not identified but not major[2]	
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not identified but not major[2]	
			Anaerobic aquatic	not identified but not major[2]	
			Field studies	not analyzed	
Unknown 3/4/7/6	Unknown compound with t_R 12.5-13.2 min that formed under irradiated conditions in the aqueous photolysis study, including unknowns 3 (phenyl-labeled) and 4 (uracil-labeled) in the pH5 study and unknowns 7 (phenyl-labeled) and 6 (uracil-labeled) in the pH7 study.	Unknown	Aerobic soil	not identified but not major[2]	
			Anaerobic soil	(data submission pending)	
			Soil photolysis	not identified but not major[2]	
			Aq. photolysis -pH5	**15** (20)	15 (20)
			Aq. photolysis -pH7	**10** (21)	10 (21)
			Hydrolysis	not identified but not major[2]	
			Aerobic aquatic	not identified but not major[2]	
			Anaerobic aquatic	not identified but not major[2]	
			Field studies	not analyzed	

1 "nd" means that the compound was not detected.

2 "not identified but not major" means that the compound was not identified and that any unidentified compounds each accounted for less than 10% of the applied.

Appendix C: Tolerance Summary Table

Table C.1. Tolerance Summary for Saflufenacil.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Correct Commodity Definition/Comments
Vegetable, legume, group 06	0.03	0.03	Vegetable, legume, group 6
Vegetable, foliage of legume, group 07	0.1	0.10	Vegetable, foliage of legume, group 7
Fruit, citrus, group 10	0.03	0.03	
Fruit, pome, group 11	0.03	0.03	
Fruit, stone, group 12	0.03	0.03	
Nut, tree, group 14	0.03	0.03	
Pistachio	-	0.03	Translated from tree nuts
Almond, hulls	0.2	0.10	
Grain, cereal, group 15	0.03	0.03	
Grain, cereal, forage, fodder and straw group 16	0.1	0.10	
Sorghum stover	0.1	-	Included in crop group 16
Cotton, undelinted seed	0.03	0.03	
Cotton, gin byproducts	0.03	0.10	
Sunflower, seed	0.7	1.0	
Grape	0.03	0.03	
Animal - Kidney	0.02	-	Individual tolerances required for each species
Animal - Liver	0.8	-	
Milk	-	0.01	
Cattle, meat	-	0.01	
Cattle, fat	-	0.01	
Cattle, liver	-	0.80	
Cattle, meat byproducts, except liver	-	0.02	
Goat, meat	-	0.01	
Goat, fat	-	0.01	
Goat, liver	-	0.80	
Goat, meat byproducts, except liver	-	0.02	
Hog, meat	-	0.01	
Hog, fat	-	0.01	
Hog, liver	-	0.80	
Hog, meat byproducts, except liver	-	0.02	
Sheep, meat	-	0.01	
Sheep, fat	-	0.01	
Sheep, liver	-	0.80	
Sheep, meat byproducts, except liver	-	0.02	
Horse, meat	-	0.01	
Horse, fat	-	0.01	
Horse, liver	-	0.80	
Horse, meat byproducts, except liver	-	0.02	

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R173760

Chemical Name: Benzamide, 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2H)-pyrimidinyl]-4-fluoro-N-[[methyl(1-methylethyl)amino]sulfonyl]-

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